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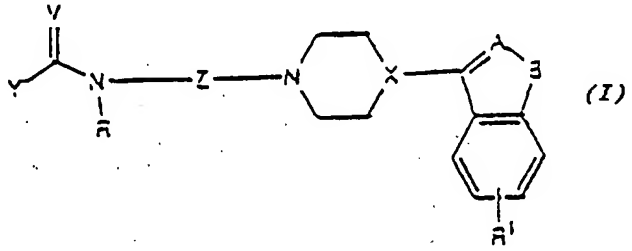
(54) Title: HETEROAROMATIC COMPOUNDS WITH ANTIPSYCHOTIC ACTIVITY

(57) Abstract

The present invention relates to a group of piperazine and piperidine derivatives of formula (I), wherein Y is a heteroaryl group optionally substituted by one or more halogen, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, aryloxy, arylC_{1-6}alkylenoxy, hydroxy, $S(O)_nR^2$ or $S(O)_nN(R^2)_2$ where n is 0, 1 or 2, CN, $CON(R^2)_2$, COR^2, CO_2R^2, CO-aryl, azido, $-N(R^2)_2$, $-NR^2N(R^{2a})_2$, $-NR^2N = C(R^{2a})_2$, $-NR^2(C = O)CH(N(R^{2a})_2)R^{2b}$, $-NR^2(C = O)R^{2a}$, $NR^2CO_2R^{2a}$, C_{1-6}alkoxycarbonylamino or PhN = N; with the proviso that Y does not include benzisothiazolyls or benzisoxazolyis, V is O or S; Z is C_{1-8}alkylene optionally interrupted by -O- or $-S(O)_n-$ where n is 0, 1 or 2, C_{2-8}alkenylene or C_{2-8}alkynylene; X is N, CR^3 or COR^3;



(I)

A is CR^4 or N; B is oxygen, NR^5 or $S(O)_n$, where n is 0, 1 or 2; and R^1 is hydrogen or one or more halogen, hydroxy, nitro, CN, NR^6_2, C_{1-6}alkoxy, aryloxy, arylC_{1-6}alkylenoxy, or COR^6, R, R^2, R^{2a}, R^{2b}, R^3, R^4, R^5 and R^6, are each hydrogen or C_{1-6}alkyl; or a salt, solvate, N-oxide or physiologically functional derivative thereof, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy, in particular in the treatment of psychotic disorders.

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HETEROAROMATIC COMPOUNDS WITH ANTIPSYCHOTIC ACTIVITY

The present invention relates to a group of piperazine and piperidine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy, in particular in the treatment of psychotic disorders.

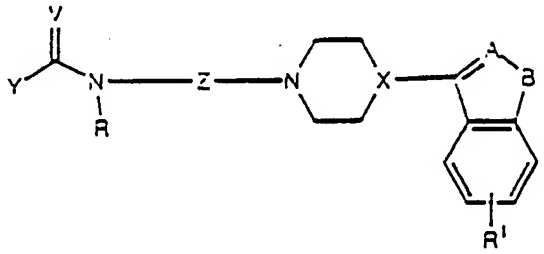
Receptors for the chemical messenger dopamine are known to be located in the striatum and the limbic brain area and such receptors have been classified as D_1 and D_2 based on receptor binding studies and on the presence or absence of a positive coupling between the receptor and adenylate cyclase activity. Activation of the D_1-receptor is associated with stimulation of adenylate cyclase, whereas the D_2-receptor mediates dopaminergic effects that do not involve direct stimulation of this enzyme [see Kebabian & Calne, Nature, , 227, 93(1979) and Harrold et al, J. Med. Chem., 30, 1631(1987)]. Although the distinct functions of the D_1- and D_2-receptors are not clear cut, a strong correlation is believed to exist between D_2-receptor antagonism and antipsychotic activity[see Seeman, Pharmacol. Rev., 32, 229(1981), Seeman et al, Biochem Pharmacol., 34, 151(1985), Creese et al, Science, 192, 481(1976) and Leysen in Clinical Pharmacology in Psychiatry: Neuroleptic and Antidepressant Research; Eds Usdin, Dahl, Gram and Lingjaerde, Macmillan: Basingstoke, pp35-52(1982)].

The chemical messenger 5-hydroxy tryptamine (5-HT) occurs widely in the central nervous system and is known to be involved in the control of behavior. A number of different 5-HT receptors and receptor sub-types have been identified. In addition to the blockade of D_2-receptors, it has been postulated that 5-HT_2 receptor antagonism is also desirable in an antipsychotic agent[see Janssen et al, J. Pharm. and Exper. Ther., 244(2), 685(1988)]. In particular it has been postulated that blockade of central dopamine D_2-receptors may control the positive symptoms of schizophrenia (e.g. delusions and hallucinations) whilst blockade of 5-HT_2 receptors may assist in the amelioration of the negative symptoms of schizophrenia (e.g. apathy and social withdrawal). It has also been suggested that blockade of the 5-HT_2 receptor results in a reduction of the extrapyramidal side effects which are known to occur in the case of neuroleptic maintenance therapy with many known antipsychotic agents.

Psychotropic benzisothiazoles and benzisoxazoles are described in US4968792, EP0357134, EP0196132 and EP0511610. Further anti-psychotic piperidines and piperazines are disclosed in EP0329168, EP0372657, EP0013612 and US5225412.

A group of novel piperazine and piperidine derivatives has been discovered that are potent antagonists of dopamine D_2 receptors and/or 5-HT_2 receptors and are therefore useful in the treatment of psychotic disorders.

The present invention provides a compound of formula (I), a salt, solvate or physiologically functional derivative thereof



(I)

wherein

Y comprises a heteroaryl group optionally substituted by one or more halogen, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, aryloxy, arylC_{1-6}alkylenoxy, hydroxy, $S(O)_nR^2$ or $S(O)_nN(R^2)_2$ where n is 0, 1 or 2, CN, $CON(R^2)_2$, COR^2, CO_2R^2, CO-aryl, azido, $-N(R^2)_2$, $NR^2N(R^{2a})_2$, $-NR^2N=C(R^{2a})_2$, $-NR^2(C=O)CH(N(R^{2a})_2)R^{2b}$, $-NR^2(C=O)R^{2a}$, $NR^2CO_2R^{2a}$, C_{1-6}alkoxycarbonylamino or PhN=N; with the proviso that Y does not include benzisothiazolyls or benzisoxazolyls;

V comprises O or S;

Z comprises C_{1-8}alkylene optionally interrupted by -O- or $-S(O)_n-$ where n is 0, 1 or 2, C_{2-8}alkenylene or C_{2-8}alkynylene;

X comprises N, CR^3 or COR^3;

A comprises CR^4 or N;

B comprises oxygen, NR^5 or $S(O)_n$, where n is 0, 1 or 2; and

R^1 comprises hydrogen or one or more halogen, hydroxy, nitro, CN, NR^6_2, C_{1-6}alkoxy, aryloxy, arylC_{1-6}alkylenoxy, or COR^6.

R, R^2, R^{2a}, R^{2b}, R^3, R^4, R^5 and R^6 herein and R^7, R^8, R^9, R^{10} and R^{11} hereinafter are hydrogen or C_{1-6}alkyl;

Compounds of formula (I) can form solvates, in particular hydrates or partial hydrates, and such solvates, including physiologically acceptable solvates, are also included within the scope of the invention.

The expression $-(R^X)_y$ should be taken to indicate the presence of y R^X variables each being independently selected and not therefore necessarily identical.

As used herein, the term "alkyl" as a group or a part of a group can be a straight or branched chain alkyl group optionally substituted by one or more halogens, hydroxy, nitro, CN, $N(R^7)_2$, C_{1-6}alkoxy or COR^7, for example, methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl or 2-methylprop-2-yl. Alkyl groups are most preferably methyl or ethyl.

As used herein, the term "alkylene" refers to a straight, branched or C_{5-6}cyclic alkylene group optionally substituted by one or more halogens, hydroxy, nitro, CN, $N(R^8)_2$, C_{1-6}alkoxy or COR^8, for example, methylene, ethylene, butylene, pentylene, hexylene, cyclohexylene, or $-(CH_2)_mC_{3-6}$cycloalkyl$(CH_2)_m-$ where m is 0 to 4, in particular where C_{3-6}cycloalkyl is a cyclopropylene group.

As used herein, the term "alkenylene" refers to a straight, branched or cyclic alkenyl group having from 4 to 8 carbon atoms optionally substituted by one or more halogens, hydroxy, nitro, CN, $N(R^9)_2$, C_{1-6}alkoxy or COR^9, such as, for example, ethenylene, propenylene, butenylene, pentenylene, hexenylene and the like.

As used herein, the term "alkynylene" refers to a straight or branched alkynyl group having from 4 to 8 carbon atoms, optionally substituted by one or more halogens, hydroxy, nitro, CN, $N(R^{10})_2$, C_{1-6}alkoxy or COR^{10} such as, for example, ethynylene, propynylene, butynylene, pentynylene, hexynylene and the like.

As used herein, the term "alkoxy" refers to an -Oalkyl, -Oalkenyl or -Oalkynyl group.

As used herein, the term "heteroaryl" refers to a monocyclic or bicyclic fused ring system comprising 5-10 atoms wherein 1 or more ring atoms are independently selected from nitrogen, oxygen or sulfur.

Bicyclic heteroaryl groups may have one of the rings with complete or partial saturation.

As used herein, the terms "aryl" refers to phenyl, naphthalenyl optionally substituted by one or more halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio or $N(R^{11})_2$.

As used herein, the terms "aryloxy", and arylC_{1-6}alkylenoxy refer to an -Oaryl and -OC_{1-6}alkylenaryl group respectively wherein "aryl" and "alkyl" are as defined hereinbefore.

As used herein, the term "halo" refers to fluoro, chloro, bromo and iodo.

As used herein, the term "physiologically functional derivative" means any physiologically acceptable ester, or salt of such ester, of a compound of formula (I) or a compound which upon administration to the recipient is capable of providing (directly or indirectly) such a compound or an active metabolite or residue thereof. Such physiologically functional derivatives can also be prodrugs of the compounds of the present invention and are considered to be within the scope of the invention.

The present invention includes all optical isomers of compounds of formula (I) and mixtures thereof including racemic mixtures. The invention also includes all geometric isomers of compounds of formula (I) including mixtures thereof.

The invention further provides compounds of formula (I) and salts, solvates and physiologically functional derivatives thereof in which the nitrogen atom shown in formula (I) which is adjacent to Z and which is part of the six-membered ring is in its oxidized form as N-oxide.

The present invention includes compounds of formula (I) in the form of physiologically acceptable salts thereof. Suitable salts are, in particular, acid addition salts including

those formed with both organic and inorganic acids. Such acids will normally be physiologically acceptable although salts of non-physiologically acceptable acids can be of utility in the preparation and purification of the compound in question. Thus preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, trifluoroacetic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. Salts of compounds of formula (I) can be made by reacting the appropriate compound in the form of the free base with the appropriate acid. Preferably the salt is the hydrochloride salt or dihydrochloride salt.

The present invention also includes within its scope compounds of formula (I) which are in the form of a salt/solvate(in particular hydrate or partial hydrate).

Base salts of the compounds of formula (I) are also included within the scope of the invention. Suitable base salts include those formed with both organic and inorganic bases. Such bases will normally be physiologically acceptable although salts of non-physiologically acceptable bases can be of utility in the preparation and purification of the compound in question. Thus preferred base salts include those formed from alkali metal(e.g., sodium), alkaline earth metal(e.g., magnesium), ammonium and quaternary ammonium.

Preferred heteroaryl groups are pyridinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, pyridazinyl, quinolinyl, isoquinolinyl, imidazolyl, benzimidazole, furyl, benzofuryl, thienyl, benzthienyl, indazolyl, oxazolyl, thiazolyl, isothiazolyl, isoxazolyl, purinyl, triazinyl, indolyl, napthiridinyl, quinazolinyl, pyrrolopyridinyl, tetrahydroquinolinyl, indolinyl, quinoxalinyl, triazolyl or thiadiazolyl.

More preferred heteroaryl groups are pyridinyl, pyrrolyl, quinolinyl, imidazolyl, furyl, thienyl, benzthienyl, indolyl, napthiridinyl, quinazolinyl, tetrahydroquinolinyl and indolinyl.

The most preferred heteroaryl groups are pyridinyl, quinolinyl, thienyl, benzthienyl, indolyl, tetrahydroquinolinyl and indolinyl

According to a preferred aspect of the present invention Y is substituted with $N(R^2)_2$.

According to a further preferred aspect of the present invention Y is pyridine, thiophene or benzthiophene optionally substituted with $N(R^2)_2$.

According to a more preferred aspect of the present invention R is H or Me, Y is pyridine, thiophene or benzthiophene optionally substituted with NH_2, NHMe or NHAc.

According to the most preferred aspect of the present invention R is H and Y is pyridine or thiophene substituted with NH_2.

According to further preferred aspect of the present invention V is more preferably O, Z is C_{1-6} alkylene and is most preferably C_4 alkylene; B is -S-, NH or -O-, is more preferably -S- or -O- and is most preferably -S-; A is CH or N and is most preferably N and R^1 is H or F and is most preferably H.

Preferred compounds of formula (I) include:
N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide;
N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide;
N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-pyridinecarboxamide;
t-Butyl-N-(4-(N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)-3-thienyl)carbamate;
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-pyridinecarboxamide;
4-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-thiophenecarboxamide;
4-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-thiophenecarboxamide;

3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)benzo(b)thiophene-2-carboxamide;
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-thiophenecarboxamide;
N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-8-quinolinecarboxamide;
N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2,3,4-tetrahydro-8-quinolinecarboxamide;
N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-2,3-dihydro-1H-indole-7-carboxamide;
N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1H-indole-7-carboxamide;
and physiologically acceptable salts, solvates physiologically functional derivatives and N-oxides thereof.

More preferred compounds of formula (I) include:
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-thiophenecarboxamide;
N-(4-(4-(1,2,Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide;
N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide;
and physiologically acceptable salts, solvates physiologically functional derivatives and N-oxides thereof.

The most preferred compound of formula (I) is:
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-pyridinecarboxamide;
and physiologically acceptable salts solvates physiologically functional derivatives and N-oxides thereof.

Salts of compounds of formula (I) are preferably the HCl salts and solvates are preferably hydrates.

The compounds of formula (I) show an advantageous profile of pharmacological activity and are useful in the treatment of a number of conditions. The compounds show, for example anxiolytic, centrally-acting muscle relaxant, and antidepressant

activity. They are also useful in the treatment of aggression associated with senile dementia, borderline personality disorders and as a broad-spectrum antiemetic. In particular the compounds are useful in the treatment of psychotic disorders such as schizophrenia.

Potential antipsychotic activity can be assessed by the ability of a compound to block apomorphine-induced climbing in the mouse[see Ogren et al, Eur. J. Pharmacol., 12, 459(1984), Iversen, Science, 188, 1084(1975) and Gudelsky & Moore, J. Neural Transm., 38, 95(1976)). The tendency of a compound to induce catalepsy and its ability to block apomorphine induced stereotypes are behavioural measures which indicate the potential of a compound to induce extrapyramidal side effects.

The compounds of formula (I) are potent antagonists at dopamine D_2 receptors and at 5-HT_2 receptors and have utility as antipsychotics. This profile of activity has been confirmed by the potency of compounds of formula (I) in the mouse-climbing assay and by good ratios of the dose required for potency in this assay to the dose required for the induction of catalepsy.

Compounds of formula (I) are also potent agonists at the $5HT_{1A}$ receptor. This activity has been associated with anti-depressant and anxiolytic effects as well as with a reduction of extrapyramidal side-effects. The combination of potent dopamine D_2 receptor antagonism and 5-HT_2 receptor antagonism with 5-HT_{1A} receptor agonism which is to be found in compounds of formula (I) is a particularly advantageous profile of activity for an anti-psychotic agent and, in particular, for a drug for use in the treatment of schizophrenia.

According to a further aspect, the present invention also provides a method for the treatment or prophylaxis in a mammal, such as a human, of a disorder selected from the following:
anxiety, muscle spasm, depression, aggression associated with senile dementia, borderline personality disorders, emesis and psychosis which comprises administering to the mammal an effective treatment amount of a compound of formula (I) or a physiologically acceptable salt, or solvate or physiologically functional derivative thereof. In particular a method for the treatment or prophylaxis in a mammal of a psychotic disorder which comprises administering to the mammal an anti-psychotic

effective treatment amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof or a physiologically functional derivative or N-oxide thereof. In particular, the invention provides such a method wherein the psychotic disorder is schizophrenia.

According to a yet further aspect, the present invention provides a compound of formula (I) or a physiologically acceptable salt or solvate thereof, or a physiologically functional derivative or N-oxide thereof for use in therapy, in particular the therapy or prophylaxis of a psychotic disorder such as schizophrenia. The invention also provides the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment or prophylaxis of a psychotic disorder such as schizophrenia.

Whilst it may be possible for the compounds of the present invention to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof or a physiologically functional derivative or N-oxide thereof together with one or more pharmaceutically acceptable carriers therefor and optionally one or more other therapeutically active ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

The compositions include those suitable for oral, parenteral (including subcutaneous, transdermal, intradermal, intramuscular and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route can depend upon for example the condition and disorder of the recipient. The compositions can conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the present invention as herein defined or a pharmacologically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired composition.

Compositions of the present invention suitable for oral administration can be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient can also be presented as a bolus, electuary or paste.

A tablet can be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets can be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets can optionally be coated or scored and can be formulated so as to provide slow or controlled release of the active ingredient therein.

Compositions for parenteral administration include aqueous and non-aqueous sterile injection solutions which can contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which can include suspending agents and thickening agents. The compositions can be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and can be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules and tablets of the kind previously described.

Compositions for transdermal administration can be delivered by passive diffusion or by electrically assisted transport, for example, iontopheresis[see, for example, Pharmaceutical Research 3 (6), 318 (1986)] and typically take the form of an optionally buffered aqueous solution of a compound of formula (I) or a salt or acid derivative thereof. Suitable compositions comprise citrate or bis/tris buffer (pH6) or ethanol/water. Such compositions can optionally comprise a lysosomal uptake-inhibiting agent.

Compositions for rectal administration can be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Compositions for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage compositions are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions of this invention can include other agents conventional in the art having regard to the type of composition in question, for example those suitable for oral administration can include flavouring agents.

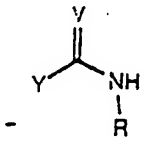
The compounds of the invention are preferably used to treat psychotic disorders such as schizophrenia by oral administration or injection (intraparenteral or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also the route of administration can vary depending on the condition and its severity.

The compounds of the invention are typically administered orally or via injection at a dose of from 0.02 to 50.0 mg/kg per day. The dose range for adult humans is generally from 1.4 to 3500 mg/day and preferably between 2.8 to 1750mg/day, more preferably 7 to 700mg/day.

The present invention also provides processes for the preparation of compounds of formula (I) and physiologically acceptable salts and solvates thereof and physioligically functional derivatives thereof. In general the compounds of formula (I) can be prepared by any process known in the prior art for the preparation of analogous compounds. In the following description, the groups Z, X, V, A, B, R, R^1, R^2, R^{2a}, R^{2b}, R^3, R^4, R^5,

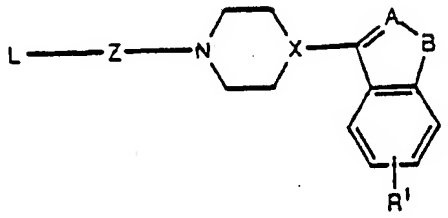
R^6, R^7, R^8, R^9, R^{10}, and R^{11}, have the meanings ascribed to them in formula (I) unless otherwise stated.

According to a first general process (A), compounds of formula (I) can be prepared by reaction of a compound of formula (II)



(II)

with a compound of formula (III)

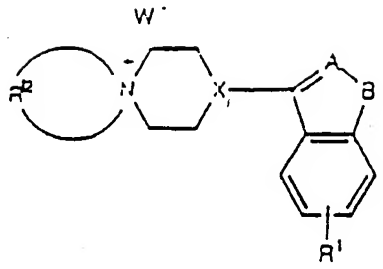


(III)

where L is a leaving group, for example, a halogen such as bromine, chlorine or iodine, an alkyl- or arylsulfonyloxy such as methanesulfonyloxy or p-toluenesulfonyloxy, in the presence of an appropriate solvent and base.

The process can be carried out either at room temperature or at elevated temperature such as 60 °C to 140 °C. Suitable solvents include N,N-dimethylformamide, acetonitrile, benzene, toluene, xylene etc. and appropriate bases can be chosen from organic bases such as triethyl amine, pyridine etc., alkali metal carbonates or bicarbonates such as sodium carbonate, potassiuim carbonate, sodium bicarbonate, potassium bicarbonate etc., or alkali metal hydrides such as sodium hydride, potassium hydride etc.

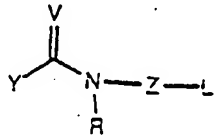
According to a second general process (B), compounds of formula (I) wherein Z is -$(CH_2)_4$-or-$(CH_2)_5$- can be prepared by reaction of a compound of formula (II) with a compound of formula (IV)



(IV)

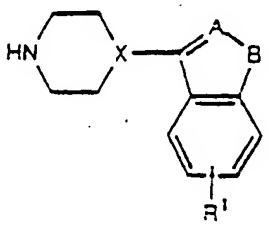
where W^- is a suitable anion, such as a halogen, for example, bromine or chlorine, sulphonic acid esters such as mesylate or tosylate and R^{12} is $-(CH_2)_4-$ or $-(CH_2)_5-$, more particularly $-(CH_2)_4-$. The conditions of reaction can be the same as those described for general process (A) above. Additionally a complexing agent such as 1,4,7,10,13,16-hexaoxacyclooctatecane(18-crown-6) can be included.

According to a third general process (C), compounds of formula (I) can be prepared by reaction of a compound of formula (V)



(V)

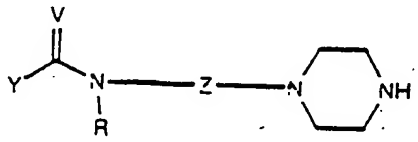
in which L is as hereinbefore defined, with a compound of formula (VI)



(VI)

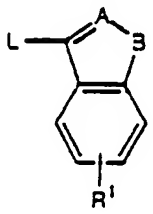
The process can be carried out as described for general process (A) above.

According to a fourth general process (D), compounds of formula (I) in which X is N can be prepared by reaction of a compound of formula (VII)



(VII)

with a compound of formula (VIII)



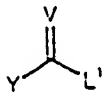
(VIII)

in which L is as hereinbefore defined.

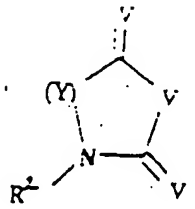
The process can be carried out as described for general process (A) above.

According to a sixth general process (F), compounds of formula (I) can be prepared by reaction of compounds of formula (IX)

(IX)

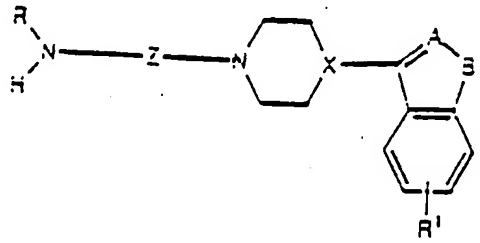


wherein L^1 is a halogen(e.g., Cl, Br), OMe or OH, or, in the case where Y in the compound of formula (I) is to be substituted at at least one of the positions ortho to the amide or thioamide with an - NHR^2 group by reaction of a compound of formula (IXa),



(IXa)

and wherein Y,V and R^2 are as previously described, with a compound of formula (X)

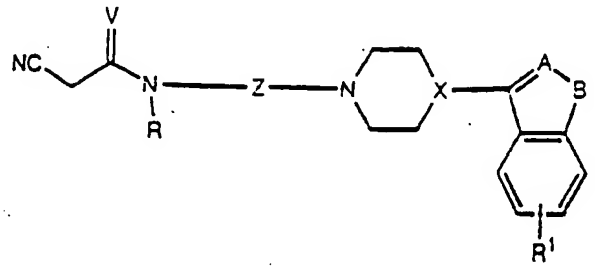


(X)

in a suitable organic solvent with or without the addition of a suitable base at or below room temperature or at elevated temperatures (e.g, -30 °C to 140 °C). Suitable solvents include N,N-dimethylformamide, acetonitrile, dichloromethane, benzene, toluene, tetrahydrofuran, xylene etc. and appropriate bases can be chosen from organic bases such as triethyl amine, pyridine etc., alkali metal carbonates or bicarbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate etc., or alkali metal hydrides such as sodium hydride, potassium hydride etc. Additionally, catalysts or coupling reagents such as trimethylaluminum, isobutylchloroformate or 1,3-dicyclohexylcarbodiimide(DCC) can also be included.

When L is OH and Y is substituted with an NHR group adjacent to the carbonyl or thiocarbonyl group, the process can be carried out in the presence of silicon tetrachloride in a refluxing solvent such as anhydrous pyridine. [Kornet, M.J. J.Heterocyclic Chem., 29, 103(1992)].

According to a seventh general process(G), compounds of formula (I) in which Y is a thiophene group can be prepared by treatment of a compound of formula (Xa)



(Xa)

with 1,4-dithiane-2,5-diol[Walser, A. et al, J. Het. Chem., 28, 1121(1991)].

Compounds of formula (I) can also be prepared from other compounds of formula (I). The following constitute examples of such interconversions.

Compounds of formula (I) in which Z is C_{2-8}alkylene can be prepared by reduction of a compound of formula (I) in which Z is C_{2-8}alkenylene or C_{2-8}alkynylene. Reduction can be achieved by catalytic hydrogenation with hydrogen in the presence of a suitable catalyst such as palladium, platinum, nickel, rhodium etc. in an appropriate solvent such as ethanol, tetrahydrofuran, methanol, ether, ethyl acetate, benzene, toluene, hexane etc. The reaction can be carried out at atmospheric or elevated pressure and at room or elevated temperatures such as 20 to 100 ^{0}C. Partial reduction of an acetylene (-C≡C-) to the alkylene (-C=C-) can be accomplished by reduction using a poisoned catalyst such as Lindlar catalyst.

Compounds of formula (I) which are optionally substituted by one or more hydroxy can be prepared from the corresponding methoxy derivatives by known methods. [For example, by treatment with a Lewis acid such as boron tribromide or aluminium trichloride in a solvent such as dichlormethane at room temperature [Mcomie, J.F.W. and West, D.E. Org. Synth. Coll. Vol. V., 412(1973)., Dillard, R.D. et al., J.Med.Chem. 34, 2768-2778(1991)].

Compounds of formula (I) which are optionally substituted by one or more $N(R^2)_2$ or $NRN(R^2)_2$ can be prepared by hydrolysis of the corresponding alkoxycarbonylamino derivatives by known methods, for example, by treatment of a (tert-butoxycarbonyl)-amino derivative with an acid such as trifluroacetic acid, and a t-butyl cation scavenger such as anisole or thiophenol in a solvent such as chloroform at room temperature [Lundt. B.F. Int. J. Prept. Protein Res. 12, 258(1978)].

Compounds of formula (I) which are optionally substituted by one or more NH_2 can also be prepared by reduction of the corresponding nitro derivatives by known methods. [For example by catalytic hydrogenation with hydrogen with a catalyst, e.g., platinum, palladium, raney nickel[Org. Synth., 49, 116(1969), J.Med.Chem., 16, 1043(1973); J.Org.Chem., 38, 60(1973)].

Compounds of formula (I) which are optionally substituted by one or more $-NR^2(C=O)R^{2a}$, $-NR^2CO_2R^{2a}$ or $-NR^2(C=O)CH(NR^{2a})_2R^{2b}$ can be prepared by acetylation of the corresponding amino derivatives by known methods. [For example by treatment with an acid chloride such as acetyl chloride or ethyl chloroformate and an organic base such as triethylamine in a solvent such as dichloromethane].

Compounds of formula (I) where R is C_{1-6} alkyl can be prepared by alkylation of the corresponding secondary amide by known methods(for example, by treatment with a base such as sodium hydride in a suitable solvent such as dimethylformamide, followed by treatment with an alkylating agent such as methyl iodide).

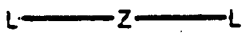
Compounds of formula (I) where V represents sulphur, can be prepared by treatment of compounds of formula (I) where V represents oxygen, with a sulfonating reagent such as Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] in a solvent such as toluene at an elevated temperature. [Synthesis, 941 (1979); Tetrahedron, 35, 2433 (1979).

Compounds of formula (I) which are optionally substituted by one or more $NHN=C(R^2)_2$ can be prepared from the corresponding hydrazine derivatives and the appropriate ketones by known methods.

Compounds of formula (I) where the nitrogen is oxidized to the N-oxide can be prepared by oxidation of compounds of formula (I) with an oxidizing reagent such as m-chloroperoxybenzoic acid in an appropriate solvent such as dichloromethane.

Compounds of formula (II) are either known compounds or can be prepared by standard methods known in the art.

Compounds of formula (III) can be prepared by alkylation of a compound of formula (VI) with a compound of formula (XI)

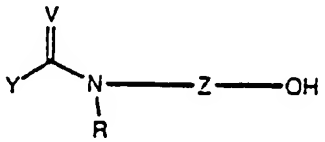


(XI)

where L is a leaving group such as for example a halogen such as bromine chlorine or iodine, an alkyl or an arylsulfonyloxy such as methanesulfonyloxy or p-toluenesulfonyloxy.

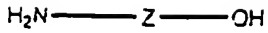
In some cases, for example when both L groups are halogen and Z is R^{12}, particularly $(CH_2)_4$, the same reaction can lead to the compound of formula (IV) [J.Med.Chem., 29, 359-369 (1986)].

Compounds of formula (V) can be prepared by alkylation of the appropriate compound of formula (II) with a compound of formula (XI). Alternatively the compound of formula (V) can be prepared by conversion of the hydroxyl group in a compound of formula (XII)



(XII)

into a leaving group, L as hereinbefore defined, by known methods. The compound of formula (XII) can in turn be prepared by condensation of a compound of formula (IX) with an amino alcohol of formula (XIII)



(XIII)

or by treatment of a compound of formula (II) with a compound of formula L-Z-OH. The process can be carried out either at room temperature or at elevated temperature such as 60 °C to 140 °C. Suitable solvents include N,N-dimethylformamide, acetonitrile, benzene, toluene, xylene etc. and appropriate bases can be chosen from organic bases such as triethyl amine, pyridine etc., alkali metal carbonates or bicarbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate etc., or alkali metal hydrides such as sodium hydride, potassium hydride etc.

Compounds of formula (VI) are either known compounds or can be prepared by know methods, for example:

when X = N, A = N and B = S:
Yevich et al, J. Med. Chem., 29, 359-69 (1986),
US 4,590,196;

when X = C, A = N and B = S:
US 4,528,292;

when X = N, A = N and B = O:
J. Med. Chem., 29, 359-69 (1986);

when X = C, A = N and B = O:
J. Med. Chem., 28, 761-69 (1985);

when X = N, A = N and B = SO_2:
J. Med. Chem., 34, 3316-3328(1991). Alternatively this intermediate can be prepared by the treatment of 3-chlorobenzisothiazole-1,1-dioxide (Eur. Pat. Appl. 0 196096) with piperazine in a solvent such as toluene at elevated temperatures such as 150-160 °C;

when X = N, A = N and B = S(O):

J. Med. Chem., 34, 3316-3328(1991);

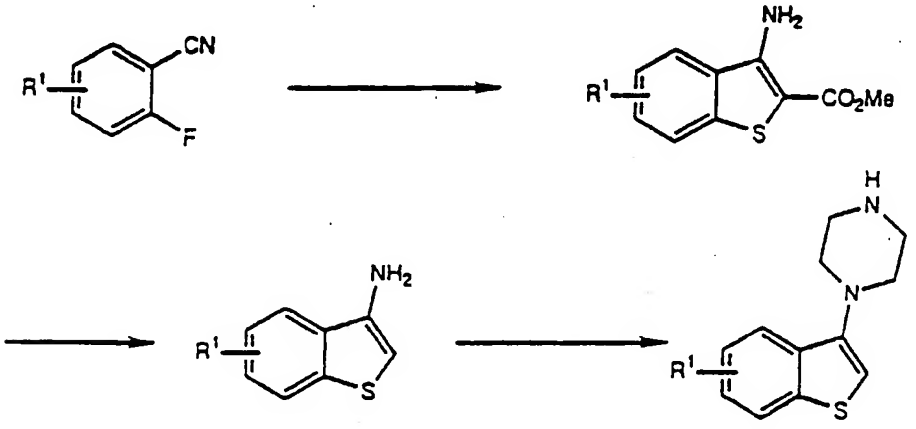
when X = C, A = C and B = NR^5:

US 4,335,127,

US 4,710,500;

when X = N, A = C and B = S:

can be prepared according to the following reaction scheme; by heating appropriately substituted aminobenzo[b]thiophenes with piperazine in a solvent such as 1-methyl-2-pyrrolidinone. The requisite aminobenzo[b]thiophenes can be prepared by treatment of appropriately substituted 2-fluorobenzonitrile with the anion of methyl thioglycolate followed by decarbomethoxylation of the resulting benzo[b]thiophene:



when X = C, A = C and B = S:

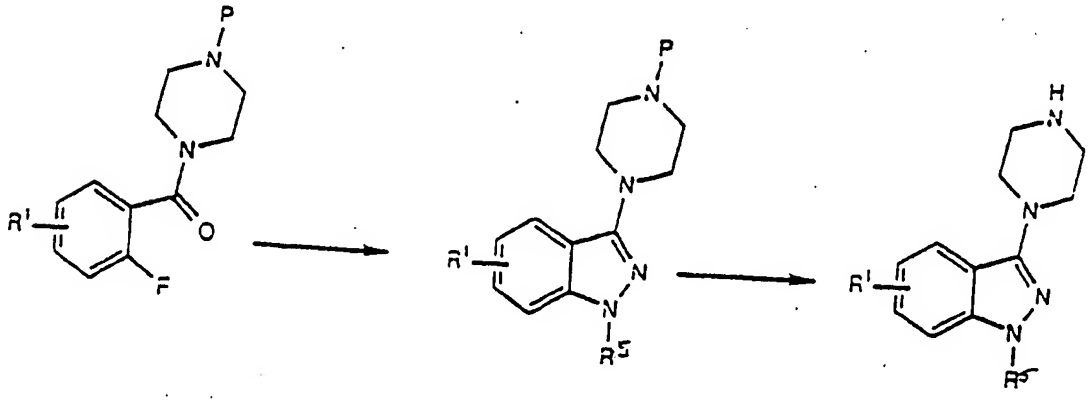
FR 2253519;

when X = N, A = N and B = NR^5:

US 4,957,916;

when X = C, A = N and B = NR^5:

can be prepared by deprotection of N-protected piperinylindazoles obtained from the reaction of an appropriately substituted 4-(2-fluoroaroyl)piperidine [J.Med.Chem., 28, 761.(1985)] with a hydrazine in a refluxing solvent such as n-butanol according to the following scheme:



when X = C, A = C and B = SO_2:

JP 03264583 A2;

when X = C, A = C and B = NR^5:

DE 3500898 A1.

Compounds of formula (VII) can be prepared by alkylation of piperazine with a compound of formula (V).

Compounds of formula (VIII) are either known compounds or can be prepared by known methods, for example:

when L is Cl, A = N and B = S:

US 4,590,196;

when L is Cl, A = N and B = O:

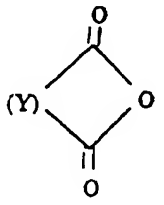
J. Med. Chem., 29, 359 (1986);

when L is Cl, A = N and B = SO_2:

EP 0196096 A2

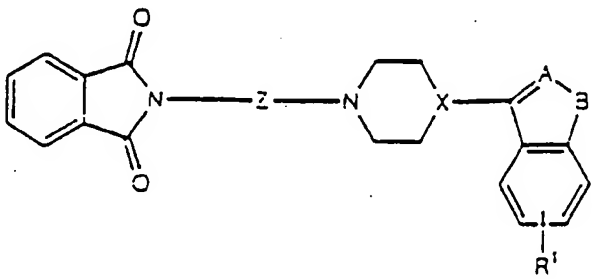
Compounds of formula (IX) or (IXa) are either known compounds or can be prepared by known methods.

For example, compounds of formula (IXa) can be prepared by the treatment of the appropriate 2-amino-substituted acids with phosgene or a phosgene substitute (e.g. trichloromethyl chloroformate) in an appropriate solvent such as benzene or dioxane [J.Het.Chem. 12, 565(1975); J.Amer.Chem.Soc., 72, 4887.(1950); J.Org.Chem. 41, 2070(1976)]. The compounds of formula (IXa) where V represents oxygen can also be prepared by treatment of the appropriately substituted anhydrides of formula (XIX) with azidotrimethylsilane in an appropriate solvent such as chloroform. The corresponding thio derivatives of the formula (IXa) where V represents sulphur can be prepared by treatment of the corresponding oxo derivative with phosphorus pentasulfide in refluxing xylenes.



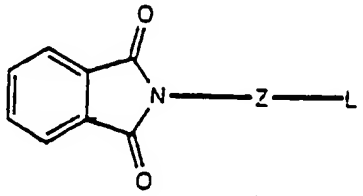
(XIX)

Compounds of formula (X) wherein R=H can be obtained by cleavage of the corresponding phthalimides of formula (Xb)



(Xb)

with hydrazine hydrate in methanol. Compounds of formula (Xb) can be prepared by the alkylation of compounds of formula (VI) with compounds of formula (XX)

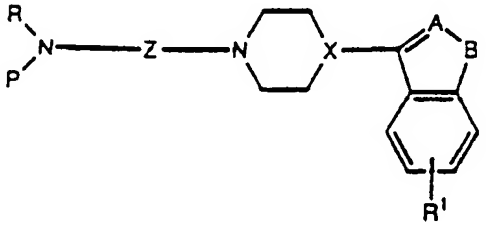


(XX)

wherein Z and L are as defined hereinbefore.

Compounds of formula (XX) are either commercially available or can be prepared by the alkylation of phthalimide with a compound of formula (XI).

Compounds of formula (X) wherein R=C_{1-6} alkyl can be prepared from compounds of formula (Xc)



(Xc)

wherein P is a protecting group, for example trifluoroacetate, by removal of the protecting group by known methods, for example aqueous potassium carbonate.

Compounds of formula (Xc) wherein R=C_{1-6} alkyl can be prepared from compounds of formula (X), wherein R=H, by protection of the amino group, for example as the trifluoroacetamide, followed by alkylation of the resulting protected amine with a C_{1-6} alkyl halide, for example methyliodide.

Compounds of formula (Xa) can be prepared by coupling compounds of formula(X) with cyanoacetic acid in the presense of a suitable coupling reagent such as 1,3-dicyclohexylcarbodiimide(DCC) in an appropriate solvent such as N,N'-dimethylformamide.

BIOLOGICAL DATA

A. Antipsychotic

Antagonism of apomorphine (5mg/kg s.c.) - induced climbing in the mouse is a measure of dopamine receptor antagonism in the mesolimbic brain region and in turn reflects potential antipsychotic activity.

Compounds were administered orally to the mice 1 hour prior to scoring. 3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl-2-pyridinecarboxamide (Example 5) antagonised apomorphine-induced climbing in the mouse at an ED_{50} = 5.7 mg/kg, p.o and 3-Amino-N-(4-(4-(1,2- benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-thiophenecarboxamide(Example 8) at an ED_{50}=9.7mg/kg p.o. [Costall, B., Naylor, R.J. and Nohria, V. Climbing behaviour induced by apomorphine in mice: A potential model for the detection of neuroleptic activity, European Journal of Pharmacology, 50, 39-50(1978)].

Pharmaceutical Compositions

The following examples illustrate the preparation of pharmaceutical compositions in which the active ingredient is a compound of formula (I) or a physiologically acceptable salt or solvate thereof, for example the compound 3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl-2-pyridinecarboxamide. These examples are not to be construed as limiting the invention.

A. Tablets

Active ingredient	150mg)
Lactose	200mg)
Maize Starch	50mg)
Polyvinylpyrrolidone	4mg)
Magnesium Stearate	4mg)

) = contents per tablet.

The active ingredient is mixed with the lactose and starch and granulated with a solution of the polyvinylpyrrolidone in water. The resultant granules are dried, mixed with magnesium stearate and compressed to give tablets.

B. Injections

Injection I

The salt of a compound according to the invention is dissolved in sterile water for injection.

Intravenous injection composition II

Active ingredient	0.20g
Sterile, pyrogen-free phosphate buffer (pH9.0) to	10ml

The active ingredient as a salt is dissolved in most of the phosphate buffer at 35-40 ^{o}C, then made up to volume and filtered through a sterile micropore filter into sterile 10ml glass vials (Type I) which are sealed with sterile closures and overseals.

C. Capsule compositions

Capsule Composition I

Composition I can be prepared by admixing the ingredients and filling two-part hard gelatin capsules with the resulting mixture.

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

Capsule Composition II

		mg/capsule
(a)	Active Ingredient	250
(b)	Macrogel 4000 BP	350
		600

Capsules can be prepared by melting the Macrogel 4000 BP, dispersing the active ingredient in the melt, and filling two-part hard gelatin capsules therewith.

Capsule Composition III (Controlled release capsule)

		mg/capsule
(a)	Active Ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose Bp	125
(d)	Ethyl Cellulose	13
		513

The controlled-release capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with ethyl cellulose (d) as a controlled-release membrane and filled into two-part hard gelatin capsules.

D. Syrup composition

Active ingredient	0.2500g
Sorbitol Solution	1.5000g
Glycerol	1.0000g
Sodium Benzoate	0.0050g
Flavour	0.0125ml
Purified Water q.s. to	5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

E. Suppository composition

	mg/suppository
Active ingredient (63ml) *	250
Hard Fat, BP (Witepsol H15 - Dynamit Nobel)	1770
	2020

* The active ingredient is used as a powder wherein at least 90% of the particles are of 63mm diameter or less.

One fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45 °C maximum. The active ingredient is sifted through a 200mm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45 °C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250mm stainless steel screen and, with continuous stirring, allowed to cool to 40 °C. At a temperature of 38-40 °C, 2.02g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

F. Transdermal Composition

Compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 20%, preferably about 3% to 15%. As one particular possibility, the active compound must be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318(1986).

The invention is further illustrated by the following Examples which are not to be construed as limiting thereof.

Experimental Section

General

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as dimethyl formamide (DMF), tetrahydrofuran (THF), dichloromethane, toluene, pyridine, and dimethyl sulfoxide (DMSO) were obtained from Aldrich Chemical Company in sure seal bottles. Triethylamine was distilled from calcium hydride prior to use. All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere. Flash chromatography [Still, W. C. et al. J. Org. Chem.,43, 2923(1978)] and Flush chromatography were performed using EM Science silica gel 60 (230-400 mesh ASTM). Thin-layer chromatography (TLC) was performed with Analtech silica gel FG TLC plates (250 mm). ^{1}H NMR and ^{13}C NMR were determined with superconducting, FT NMR spectrometers operating at 200, 300, and 500 MHz. Chemical shifts are expressed in ppm downfield from internal trimethylsilane. Significant ^{1}H NMR data are reported in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in Hz. Elemental analyses were performed by either Atlantic Microlab, Inc., Norcross Georgia, or Galbraith Laboratories, Inc., Knoxville, Tennessee. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. The piperazine

benzisothiazole intermediate. 3-(1-piperazinyl)- 1,2-benzisothiazole was prepared according to known procedures[Yevich, J.P. et al. J.Med.Chem., 29, 359-369(1986)].

Examples

Example 1

(a) Preparation of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl) phthalimide hydrochloride.

N-(4-Bromobutyl)phthalimide (3.50 g, 0.0124 mol), 3-(1-piperazinyl)-1,2-benzisothiazole (2.72 g, 0.0124 mol, 1.0 eq), triethylamine (2.24 mL, 0.0161 mol, 1.3 eq) and acetonitrile (15.0 mL) were added to a 100-mL, round-bottomed flask. The cloudy orange solution was heated under N_2 at reflux for 17 h. The mixture was allowed to cool to room temperature and diluted with dichloromethane. The organic solution was washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give 5.48 g of a light orange solid. This crude material was recrystallized from acetonitrile and dried in a vacuum oven to give 4.35 g of a tan powder. The hydrochloride salt was prepared by the addition of 1N HCl in ether and recrystallized from 95% ethanol to give 4.53 g (82%) of the title compound as an off-white powder. mp: 258-260 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.72 (m, 4), 3.20 (m, 4), 3.54 (m, 6), 4.02 (br d, 2, J = 13.7), 7.44 (ddd, 1, J = 8.1, 7.0, 1.1), 7.57 (ddd, 1, J = 8.1, 7.0, 1.0), 7.85 (m, 4), 8.09 (dd, 2, J = 8.0, 4.5), 11.18 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.52, 25.25, 36.82, 46.30, 50.44, 54.98, 121.13, 122.98, 123.94, 124.56, 126.90, 128.06, 131.58, 134.33, 152.04, 162.16, 167.93.

Anal. Calcd for $C_{23}H_{24}N_4O_2S \cdot HCl$: C, 60.45; H, 5.51; N, 12.26. Found: C, 60.46; H, 5.55; N, 12.17.

(b) Preparation of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole.

Hydrazine hydrate (Aldrich Chemical Company,85%)(2.62 g, 1.5 eq) was added to a solution of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)phthalimide (12.46 g, 0.0296 mol) in methanol (30.0 mL). The reaction mixture was heated at reflux for 3.5 h and allowed to cool to room temperature. 1N HCl (59.0 mL) was added to the solution and the resulting white precipitant was filtered and washed with water. The filtrate was made basic by the addition of 50% NaOH and extracted with dichloromethane. The

organic layer was dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 8.1 g (94%) of the title compound as an orange-brown oil. ^1H NMR ($CDCl_3$): d 1.38 (br s, 2), 1.55 (m, 4), 2.45 (t, 2, J = 7.4), 2.68 (t, 4, J = 5.0), 2.74 (t, 2, J = 6.8), 3.57 (t, 4, J = 5.0), 7.35 (ddd, 1, J = 1.1, 7.0, 8.1), 7.46 (ddd, 1, J = 1.1, 7.0, 8.1), 7.81 (d, 1, J = 8.1), 7.91 (d, 1, J = 8.2). This crude amine was used without further purification.

(c) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide hydrochloride

Nicotinoyl chloride hydrochloride (Aldrich Chemical Company) (1.1 g, 6.1 mmol) was added portion-wise to an ice-cold, stirred solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.8 g, 6.0 mmol) and triethylamine (2.5 mL, 17.9 mmol, 3.0 eq) in dichloromethane (25.0 mL). The resulting suspension was allowed to stir at 0 °C for 0.5 h and at room temperature for 2 h. The cloudy reaction mixture was diluted with dichloromethane (25.0 mL) and washed with saturated $NaHCO_3$ (2 X 50 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator to give an off-white foam. The crude material was dissolved in isopropanol (20.0 mL), chilled with an ice water bath and treated dropwise with HCl (6.0 ml of a 1N solution in ether) with swirling. The mixture was diluted with ether (40.0 mL) and the resulting off-white solid was filtered and washed with ether (3 X 10 mL). The salt was recrystallized from 95% ethanol to give 1.47 (57%) of the title compound as off-white crystals. mp: 229-231 °C. ^1H NMR (DMSO-d_6): δ 1.64 (m, 2), 1.81 (m, 2), 3.27 (m, 4), 3.47 (m, 2), 3.62 (br d, 2, J = 11.5), 4.10 (br d, 2, J = 13.1), 7.56 (m, 2), 7.62 (t, 1, J = 7.6), 8.14 (t, 2, J = 6.8), 8.23 (d, 1, J = 6.2), 8.73 (d, 1, J = 4.5), 8.81 (br t, 1, J = 6.2), 9.05 (s, 1), 10.82 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.76, 27.33, 39.58, 47.53, 51.61, 56.25, 122.35, 124.57, 125.16, 125.78, 128.11, 129.28, 131.10, 136.15, 149.55, 152.88, 153.26, 163.39, 165.92. Mass spec (CI/CH_4, 50 mA/sec), m/z: M + 1 (396).

Anal. Calcd for $C_{21}H_{25}N_5OS \cdot HCl$: C, 58.39; H, 6.07; N, 16.21; S, 7.42; Cl, 8.21. Found: C, 58.37; H, 6.12; N, 16.14; S, 7.49; Cl, 8.14.

Example 2

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-pyridinecarboxamide hydrochloride

This compound was prepared, according to the method described in Example (1(c)), by employing isonicotinoyl chloride hydrochloride (Aldrich Chemical Company) (1.1 g, 6.1 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (Example 1(b)) (1.8 g, 6.0 mmol) and triethylamine (2.5 mL, 17.9 mmol, 3.0 eq) in dichloromethane (25.0 mL). The crude hydrochloride salt was recrystallized from 95% EtOH to give 1.20 g (46%) of the title compound as off-white crystals. mp: 238-240 °C. ^{1}H NMR (DMSO-d6): δ 1.64 (m, 2), 1.80 (m, 2), 3.29 (m, 4), 3.46 (m, 2), 3.61 (br d, 2, J = 10.5), 4.10 (br d, 2, J = 10.5), 7.49 (t, 1, J = 7.6), 7.62 (t, 1, J = 7.6), 7.80 (d, 2, J = 5.8), 8.15 (t, 2, J = 6.7), 8.75 (d, 2, J = 5.8), 8.90 (br t, 1, J = 5.5), 10.80 (br s, 1). ^{13}C NMR (DMSO-d6): δ 21.76, 27.24, 39.68, 47.53, 51.61, 56.24, 122.36, 122.45, 125.17, 125.78, 128.11, 129.28, 142.56, 151.30, 153.26, 163.39, 165.78. Mass spec (CI/CH_4, 50 mA/sec), m/z: M + 1 (396).

Anal. Calcd for $C_{21}H_{25}N_5OS \cdot HCl$: C, 58.39; H, 6.07; N, 16.21; S, 7.42; Cl, 8.21. Found: C, 58.47; H, 6.11; N, 16.12; S, 7.38; Cl, 8.15.

Example 3

(a) Preparation of N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide hydrochloride

Picolinic acid (1.2 g, 9.7 mmol) (Aldrich Chemical Company) and potassium hydroxide (0.56 g, 10.0 mmol) were dissolved in distilled water (25.0 mL). The water was removed with a rotary evaporator and the resulting white solid residue was treated with benzene (25.0 mL). The solution was concentrated and dried under high vacuum. The resulting potassium salt was suspended in benzene (15.0 mL) and cooled in an ice water bath. Oxalyl chloride (1.0 mL, 11.5 mmol) was added dropwise to this cooled solution. The reaction mixture was allowed to warm to room temperature and gradually to warm to a gentle reflux. The resulting wine-red black solution was cooled and added dropwise to a cooled solution (ice water bath) of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (Example 1(b)) (3.0 g, 10.0 mmol), and triethylamine (2.5 mL, 17.9

mmol), in dichloromethane (10.0 mL). The reaction mixture was allowed to warm to room temperature and stir overnight. The dark suspension was concentrated with a rotary evaporator to give a black oil. The residue was dissolved in dichloromethane and washed with saturated $NaHCO_3$. The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 5.01 g of a dark oil. The crude material was purified by chromatography on flash silica gel with a gradient eluant chloroform (100%)/chloroform-acetone-methanol (28:2:1)/chloroform-acetone-methanol (14:2:1) to give 1.80 g of the free amine. The product was taken up in dichloromethane, treated with HCl (4.6 mL of a 1N solution in ether) and diluted with ethyl acetate. A dark colored precipitate was filtered from the solution and the filtrate was allowed to stand for three days. The crystals that formed upon standing were filtered and dried to give 1.15 g (27%) of the title compound as off-white crystals. mp: 231-234 °C. ^1H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.76 (m, 2), 3.18-3.38 (m, 8), 3.57 (m, 2), 4.10 (m, 2), 7.47 (tm, 1, J = 7.6), 7.61 (m, 2), 8.02 (m, 2), 8.12 (t, 2, J = 8.1), 8.65 (dt, 1, J = 4.7, 1.2), 8.92 (t, 1, J = 6.2), 10.30 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.79, 27.54, 39.31, 47.51, 51.61, 56.32, 122.36, 123.02, 125.15, 125.78, 127.61, 128.10, 129.28, 138.94, 149.50, 151.16, 153.24, 163.37, 165.04. Mass spec (CI/CH_4 50 mA/sec), m/z: M + 1/base (396).

Anal. Calcd for $C_{21}H_{25}N_5OS \cdot HCl$: C, 58.39; H, 6.07, N, 16.21; S, 7.42; Cl, 8.21. Found: C, 58.10; H, 6.10; N, 16.04; S, 7.39; Cl, 8.09.

Examples 4 and 5

(a) Preparation of 3-azaisatoic anhydride and 6-azaisatoic anhydride

A 2:1 mixture of 3- and 6-azaisatoic anhydride was obtained from 2,3-pyridinedicarboxylic anhydride (Aldrich Chemical Company) (11.4 g, 76 mmol), azidotrimethylsilane (Aldrich Chemical Company) (11.4 mL, 86 mmol, 1.1 eq), and chloroform (50.0 mL) according to the method described by D. J. Le Court and D. J. Dewsbury, Synthesis, 11, 972(1982). The precipitant obtained from the reaction mixture was filtered and dried to give 6.10 g (48%) of a 2:1 mixture of the title compounds as a white solid. mp: 207-210 °C (dec). ^1H NMR data for the 6-isomer(minor) are given in square brackets, [ ]. ^1H NMR (DMSO-d_6): δ 7.29 (dd, 1, J = 4.9, 7.8), [7.53 (dd, 1, J = 1.5, 8.6)], [7.69 (dd, 1, J = 4.5, 8.6)], 8.29 (dd, 1, J = 1.8,

7.8), [8.49 (dd, 1, J = 1.5, 4.5)], 8.64 (dd, 1, J = 1.8, 4.9), [11.53 (br s, 1)], 12.53 (br s, 1).

(b) Preparation of 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide hydrochloride and 3-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide hydrochloride

A 2:1 mixture of 3-azaisatoic anhydride and 6-azaisatoic anhydride (1.0 g, 6.1 mmol) was added to a stirred solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (Example 1(b)) (1.8 g, 6.0 mmol) in tetrahydrofuran (20.0 mL). The reaction mixture was allowed to stir under nitrogen at room temperature for 0.5 h. The solvent was removed with a rotary evaporator, and the resulting crude residue was purified by chromatography on flash silica gel with a gradient eluant: dichloromethane (100%)/dichloromethane-methanol (98.5:1.5)/dichloromethane-methanol (97:3)/dichloromethane:methanol (93:7) to give 1.48 g (91%) of 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide as a foam and 0.54 g (66%) of 3-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide as a foam. The hydrochloride salts of each isomer were prepared independently by dissolving the free amine in dichloromethane (20.0 mL), filtering, and treating the filtrate with HCl (1 equiv. of a 1N solution in ether). The solutions were diluted with ethyl acetate and allowed to stir at room temperature for 1 h. The resulting white crystals were collected by filtration and dried in a vacuum oven to give the corresponding hydrochloride salts.

Example 4: 2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide hydrochloride. TLC: silica gel, methanol/chloroform 1:9 (R_f = 0.25). mp: 220-222 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.75 (m, 2), 3.32 (m, 8), 3.57 (m, 2), 4.08 (m, 2), 6.60 (dd, 1, J = 4.8, 7.7), 7.10 (s, 2) 7.47 (t, 1, J = 7.6), 7.60 (t, 1, J = 7.5), 7.93 (dd, 1, J = 0.8, 7.6), 8.07 (dd, 1, J = 1.3, 4.7), 8.12 (t, 2; J = 8.0), 8.54 (br t, 1, J = 5.5), 10.55 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.84, 26.30, 38.45, 46.62, 50.71, 55.38, 110.97, 111.59, 121.51, 124.32, 124.94, 127.28, 128.45, 138.10, 149.18, 152.47, 158.05, 162.58, 167.33. Mass spec (CI/CH_4, 50 mA/sec), m/z: M + 1 (411).

Anal. Calcd for $C_{21}H_{26}N_6OS \cdot HCl$: C, 56.43; H, 6.09; N, 18.80; S, 7.17; Cl, 7.93. Found: C, 56.36; H, 6.14; N, 18.75; S, 7.19; Cl, 8.03.

Example 5: 3-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide hydrochloride. TLC: silica gel, methanol/chloroform 1:9, (R_f = 0.47). mp: 238-240 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2) 1.74 (m, 2), 3.30 (m, 8), 3.58 (m, 2), 4.08 (m, 2), 6.84 (br s, 2), 7.15 (dd, 1, J = 1.4, 8.4), 7.24 (dd, 1, J = 4.2, 8.4), 7.47 (tm, 1, J = 8.0), 7.60 (tm, 1, J = 8.0), 7.79 (dd, 1, J = 1.4, 4.2), 8.12 (t, 2, J = 8.2), 8.69 (br t, 1, J = 6.2), 10.40 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.77, 26.55, 37.68, 46.47, 50.56, 55.29, 121.27, 124.07, 124.53, 124.70, 127.02, 127.24, 128.19, 128.91, 135.49, 146.32, 152.17, 162.28, 167.56. Mass spec (CI/CH_4, 50 mA/sec), m/z: M + 1 (411).

Anal. Calcd for $C_{21}H_{26}N_6OS$ • HCl: C, 56.43; H, 6.09; N, 18.80; S, 7.17; Cl, 7.93. Found: C, 56.36; H, 6.12; N, 18.70; S, 7.12; Cl, 7.85.

Examples 6 and 7

(a) Preparation of 4-azaisatoic anhydride and 5-azaisatoic anhydride

Anhydrous chloroform (50.0 mL), 3,4-pyridinedicarboxylic anhydride (11.5 g, 77.1 mmol) and azidotrimethylsilane (10.1 g, 88.0 mmol, 1.14 eq) were added to a 250-mL, round-bottomed flask and placed under N_2. The resulting creamy suspension was gently warmed to initiate the reaction. The reaction was exothermic and nitrogen gas was evolved. After 10 min the gas evolution subsided and the solution was heated at reflux for 0.75 h. As the reaction proceeded the solids dissolved, resulting in a clear pale yellow solution. The reaction mixture was allowed to cool to room temperature and ethanol (4.5 mL, 77.1 mmol, 1.0 eq) was added in one portion. Solids immediately precipitated out of solution upon this addition. The mixture was allowed to stir at room temperature for 15 min and the solids were filtered, washed with chloroform and dried in a vacuum oven at room temperature to give 12.6 g of a light yellow powder. This material was stirred with acetonitrile (100 mL) and the undissolved solids were filtered. The filtrate was heated at reflux for 0.5 h. The solution was allowed to cool to room temperature and cooled further in an ice bath the solids that formed were filtered and the filtrate was concentrated with a rotary evaporator to give 1.80 g of a yellow powder. A second crop of product was obtained by triturating all of the undissolved solids in

boiling acetonitrile (100 mL) for 1.5 h. The mixture was filtered hot and the filtrate was concentrated to provide an additional 3.35 g (41 % total) of the title compounds as yellow solids. The crude product was 1:1 mixture of 4- and 5-azaisatoic anhydride as indicated by integration of the corresponding signals in the ^{1}H NMR. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.08 (d, 1, J = 5.6), 7.80 (dd, 1 J = 4.8, 0.7), 8.45 (d, 1, J = 4.8), 8.54 (s, 1), 8.66 (d, 1, J = 5.6), 8.96 (s, 1), 12.08 (br s, 2). This material was used without further purification.

(b) Preparation of 3-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-pyridinecarboxamide dihydrochloride hydrate and 4-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide dihydrochloride

A 1:1 mixture of 4-azaisatoic anhydride and 5-azaisatoic anhydride (4.71 g, 28.7 mmol) was added to a stirred solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (Example 1(b)) (8.33 g, 28.7 mmol, 1.0 eq) in anhydrous tetrahydrofuran (40 mL). The reaction mixture was allowed to stir under nitrogen at room temperature for 1 h. The solvent was removed with a rotary evaporator, and the resulting crude residue was purified by chromatography (2 x) on flash silica gel : once with 5:95 methanol:dichloromethane and 0.1 % triethylamine as eluant and once with 3:97 methanol:dichloromethane and 0.1 % triethylamine as eluant to give 3.11 g (26 %) of 3-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-pyridinecarboxamide as a tan powder (TLC: silica gel, methanol/dichloromethane 95:5, Rf = 0.44) and 2.99 g (24 %) of 4-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide as an orange solid (TLC: silica gel, methanol/dichloromethane 95:5, Rf = 0.32). The hydrochloride salts of each isomer were prepared independently by treatment with 1N ethereal HCl. The salts were recrystallized from either ethanol/ether/EtOAc or 95 % ethanol and dried in a vacuum oven.

Example 6: 3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-pyridinecarboxamide dihydrochloride hydrate. mp: 229-231 °C. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 1.61 (m, 2) 1.83 (m, 2), 3.25 (m, 6), 3.55 (m, 4), 4.06 (br d, 2, J = 13.2), 7.46 (t, 1, J = 7.6), 7.59 (dt, 1, J = 8.1, 0.8), 8.04 (s, 2), 8.12 (t, 1, J = 8.1), 8.31 (s, 1), 9.24 (br t, 1, J = 4.4), 11.45 (br s, 1). ^{13}C NMR (DMSO-d$_6$, 50.29 MHz): δ 20.73,

26.05. 38.47. 46.54. 50.64. 55.26. 121.51. 124.32. 124.93. 126.48. 126.40. 127.02. 127.28. 128.44. 130.62. 146.83. 152.46. 162.59. 165.43.

Anal. Calcd for $C_{21}H_{26}N_6OS \cdot 2HCl \cdot 0.5\ H_2O$: C. 51.22; H. 5.94; N. 17.07; Cl, 14.40; H_2O, 1.82. Found: C. 51.02; H, 6.05; N. 16.98; Cl, 14.09; H_2O, 1.54..

Example 7: 4-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide dihydrochloride. mp: 122-130 °C (effervesces). ^1H NMR (DMSO-d_6, 200 MHz): δ 1.64 (m, 2) 1.79 (m, 2), 3.07 (m, 2), 3.30 (m, 8), 3.74 (br s, 2), 6.93 (d, 1, J = 6.6), 7.48 (t, 1, J = 7.5), 7.61 (t, 1, J = 8.7.4), 8.12 (m, 1), 8.44 (br d, 2), 8.74 (s, 1), 8.97 (br t, 1, J = 5.6), 12.40 (br s, 1). ^{13}C NMR (DMSO-d_6, 50.29 MHz): δ 21.12, 26.07, 38.30, 46.95, 50.83, 55.51, 111.05, 111.14, 121.22, 124.07, 124.64, 127.06, 128.13, 141.52, 142.36, 152.11, 157.68, 162.50, 165.22.

Anal. Calcd for $C_{21}H_{26}N_6OS \cdot 2HCl$: C, 52.17; H, 5.84; N, 17.38. Found: C, 52.25; H, 6.17; N, 17.31.

Example 8

(a) Preparation of 3-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-thiophenecarboxamide hydrochloride

3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.83 g, 9.75 mmol) (Example 1(b)) and anhydrous chloroform (50 mL) were added to a 250-mL, round-bottomed flask, and stirred under N_2. Trimethylaluminum (9.8 mL, 19.6 mmol, 2.01 eq) (Aldrich Chemical Company, 2.0 M in toluene) was added dropwise and the reaction mixture was stirred for 0.5 h. A solution of methyl-3-amino-2-thiophenecarboxylate (1.66 g, 10.56 mmol, 1.08 eq) (Aldrich Chemical Company) in anhydrous chloroform (25 mL) was added and the orange solution was heated at 45-50 °C for 5 d. The reaction mixture was slowly added to cold 1 N hydrochloric acid (100 mL). The pH of the mixture was adjusted to pH = 10 with saturated K_2CO_3 and the mixture was transferred to a separatory funnel. Chloroform was added to the separatory funnel and the layers were separated. The organic layer was washed with water (2 x 200 mL). The aqueous layers were combined and extracted with chloroform. The organic layers were combined, washed with saturated NaCl, dried over $MgSO_4$, filtered and concentrated to

give 6.53 g of the crude product as a thin dark brown-orange oil. The free base was purified by flash chromatography with dichloromethane followed by dichloromethane : methanol (95 : 5) to give 1.32 g of a tan solid. The free base (1.23 g, 3.06 mmol) was dissolved in dichloromethane and 1 N ethereal HCl (3.06 mL, 1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol / water to give 0.93 g (21%) of the title compound as a tan solid. mp: 230-232 °C. ^{1}H NMR (DMSO-d_6): δ 1.54 (m, 2), 1.75 (m, 2), 3.26 (m, 6), 3.48 (m, 2), 3.61 (br d, 2, J = 11.1), 4.10 (br d, 2, J = 12.5), 6.42 (br s, 1), 6.60 (d, 1, J = 5.3), 7.40 (d, 1, J = 5.3), 7.55 (m, 2), 8.15 (br t, 2, J = 6.9), 10.51 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.65, 27.61, 38.86, 47.40, 51.48, 56.24, 102.19, 121.90, 122.16, 124.97, 125.62, 127.92, 128.59, 129.12, 153.06, 154.08, 163.18, 165.53.

Anal. Calcd for $C_{20}H_{25}N_5OS_2$ • HCl: C, 53.14; H, 5.80; N, 15.49. Found: C, 53.23; H, 5.86; N, 15.36.

Example 9

(a) Preparation of methyl 4-((tert-butoxycarbonyl)amino)-3-thiophenecarboxylate

Methyl-4-aminothiophene-3-carboxylate hydrochloride (6.57 g, 33.9 mmol) (Maybridge Chemical Company), 1,4-dioxane (25 mL) and 5% Na_2CO_3 (25 mL) were combined in a 500 mL, round-bottomed flask, and the mixture was cooled in an ice-water bath. A solution of di-tert-butyl dicarbonate (18.6 g, 85.2 mmol, 2.51 eq) (Aldrich Chemical Company) in 1,4-dioxane (25 mL) was slowly added to the reaction mixture. The ice-water bath was removed and the reaction mixture was allowed to warm to room temperature for 18 h. An additional portion of di-tert-butyl dicarbonate (3.86 g, 17.7 mmol, 0.52 eq) in 1,4-dioxane (10 mL) was added and the reaction mixture was stirred at room temperature for 26 h. The reaction mixture was transferred to a separatory funnel. Water and ethyl acetate were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed twice with water, dried over $MgSO_4$, filtered and concentrated to give a red-brown liquid. The crude product was partially purified by flash chromatography with a gradient eluant of hexanes (100-95%) : ethyl acetate (0-5%) to give a colorless liquid. The title compound precipitated upon standing to give

2.09 g (24%) of the desired product. mp: 100-102 °C. ^{1}H NMR (DMSO-d6, 60 °C): δ 1.48 (s, 9), 3.84 (s, 3), 7.53 (d, 1, J = 3.5), 8.32 (d, 1, J = 3.5), 9.01 (br s, 1). ^{13}C NMR (CDCl3): d 28.69, 52.27, 80.94, 107.74, 121.74, 132.96, 137.74, 153.49, 164.78.

Analysis Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.28; H, 5.90; H, 5.48.

(b) Preparation of 4-((tert-butoxycarbonyl)amino)-3-thiophenecarboxylic acid

Methyl 4-((tert-butoxycarbonyl)amino)-3-thiophenecarboxylate (2.08 g, 8.08 mmol), 95% ethanol (40 mL) and 50% sodium hydroxide (10 mL) were added to a 500-mL, round-bottomed flask, and heated at 45 °C for 1 h. The reaction mixture was allowed to cool and the pH was adjusted to pH = 2 by the addition of 1 N HCl. The reaction mixture was transferred to a separatory funnel and extracted with dichloromethane. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give a white solid. The product was dried a second time, as described above, and dried in a vacuum oven, to give 1.83 g (93%) of the title compound as a white solid. mp: 167-168 °C (effervesces). ^{1}H NMR (DMSO-d6): δ 1.50 (s, 9), 7.54 (br d, 1, J = 3.3), 8.32 (d, 1, J = 3.5), 9.31 (br s, 1). ^{13}C NMR (DMSO-d6): δ 28.85, 81.07, 108.30, 122.83, 134.94, 137.35, 152.89, 166.20.

Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76. Found: C, 49.30; H, 5.44; N, 5.72.

(c) Preparation of t-butyl N-(4-(N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)-3-thienyl)carbamate

4-((tert-Butoxycarbonyl)amino)-3-thiophenecarboxylic acid (1.49 g, 6.12 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.09 g, 7.20 mmol, 1.18 eq) (Example 1(b)) and anhydrous N, N-dimethylformamide (20 mL) were combined in a 500-mL, round-bottomed flask. A solution of 1,3-dicyclohexylcarbodiimide (1.60 g, 7.75 mmol, 1.27 eq) (Aldrich Chemical Company) in anhydrous N, N-

dimethylformamide (5 mL) was added dropwise to the reaction mixture and the solution was stirred under N_2 for 0.25 h. 1-Hydroxybenzotriazole hydrate (1.0 g, 7.40 mmol, 1.21 eq) (Aldrich Chemical Company) was added to the solution and the reaction mixture was stirred under N_2 at room temperature for 2.75 d. The suspension was filtered and the filtrate was concentrated to give an orange oil. The crude free base was dissolved in dichloromethane and the solution was transferred to a separatory funnel. The organic phase was washed with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, washed with saturated NaCl, dried over $MgSO_4$, filtered and concentrated to give an orange oil. The free base was partially purified by flash chromatography with dichloromethane followed by dichloromethane : methanol (96 : 4) as eluant to give a cloudy orange oil. The oil was dissolved in dichloromethane, filtered and concentrated to give a less cloudy orange oil. The crude free base was dissolved in ethyl acetate, filtered and concentrated to give 2.73 g (86%) of the free base as a clear orange oil. A portion of the free base was isolated as the hydrochloride salt upon recrystallization from ethanol. mp: 116-119 °C. ^{1}H NMR (DMSO-d6): δ 1.44 (s, 9), 1.60 (m, 2), 1.78 (m, 2), 3.29 (m, 6), 3.44 (tm, 2, J = 12.1), 3.57 (d, 2, J = 11.9), 4.05 (d, 2, J = 13.4), 7.45 (t, 1, J = 7.6), 7.49 (br s, 1), 7.58 (t, 1, J = 7.5), 8.09 (d, 1, J = 8.2), 8.12 (d, 1, J = 8.4), 8.35 (d, 1, J = 3.4), 8.82 (br t, 1, J = 5.6), 10.17 (s, 1), 10.63 (br s, 1). ^{13}C NMR (DMSO-d6): δ 21.58, 27.02, 28.89, 38.89, 47.36, 51.47, 56.06, 80.62, 107.69, 122.16, 124.85, 124.97, 125.59, 127.93, 129.09, 129.35, 137.81, 153.01, 153.09, 163.18, 164.89.

Anal. Calcd for $C_{25}H_{33}N_5O_3S_2 \cdot HCl \cdot H_2O$: C, 52.66; H, 6.36; N, 12.28; H_2O, 3.16. Found: C, 52.76; H, 6.36; N, 12.38; H_2O, 2.90.

Example 10

(a) Preparation of 4-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-thiophenecarboxamide hydrochloride

t-Butyl N-(4-(N-(4-(4(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)-3-thienyl)carbamate (3.13 g, 6.07 mmol) (Example 9(c)), trifluoroacetic acid (24 mL) (EM Science), anhydrous anisole (6.4 mL) (Aldrich Chemical Company) and anhydrous

chloroform (50 mL) were combined in a 250-mL, round-bottomed flask, and stirred under N_2 at room temperature for 20 min. Thin layer chromatography indicated that the reaction was complete. The reaction mixture was concentrated to give an orange liquid. The crude product was dissolved in dichloromethane and transferred to a separatory funnel. The organic phase was washed with saturated $NaHCO_3$ and separated. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give an orange liquid. The crude free base was purified by flash chromatography with dichloromethane followed by dichloromethane : methanol (96 : 4) as eluant to give 1.57 g of the free base as a pale orange oil. The free base 1.40 g (3.37 mmol) was dissolved in ethyl acetate and 3.4 mL of 1 N ethereal HCl (1.0 eq) was added. The hydrochloride salt was filtered and dried to give 1.01 g (37%) of the title compound as an off-white solid. mp: 204-206 °C. ^1H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.79 (m, 2), 3.00-3.80 (m, 10), 4.04 (m, 2), 5.80 (br s, 2), 6.10 (d, 1, J = 3.3), 7.49 (ddd, 1, J = 1.0, 7.0, 8.1), 7.62 (ddd, 1, J = 1.0, 7.0, 8.1), 8.03 (d 1, J = 3.5), 8.15 (br t, 2, J = 6.8), 8.40 (br t, 1, J = 5.5). ^{13}C NMR (DMSO-d_6): δ 21.70, 27.29, 38.70, 47.46, 51.51, 56.16, 97.85, 122.18, 124.98, 125.59, 125.87, 127.93, 128.16, 129.09, 148.60, 153.06, 163.24, 165.04.

Anal. Calcd for $C_{20}H_{25}N_5OS_2 \cdot HCl$: C, 53.14; H, 5.80; N, 15.49. Found: C, 53.20; H, 5.84; N, 15.34.

Example 11

(a) Preparation of methyl 3-aminobenzo[b]thiophene-2-carboxylate

This compound was prepared according to the method of J.R. Beck[J. Org. Chem., 37, 3224(1972)] by employing 2-nitrobenzonitrile (50.0 g, 0.338 mol) (Aldrich Chemical Company), methyl thioglycolate (33.2 mL, 36.4 g, 0.343 mmol, 1.11 eq) (Aldrich Chemical Company), N,N-dimethylformamide (400 mL) and aqueous KOH (37.4 g/187 mL water) to give 36.1 g (52%) of the title compound as a pale beige solid. ^1H NMR ($CDCl_3$): 3.90 (s, 3), 5.92 (br s, 2), 7.37 (ddd, 1, J = 1.3, 7.0, 8.2), 7.48 (ddd, 1, J = 1.5, 7.0, 8.2), 7.64 (ddd, 1, J = 0.8, 1.5, 8.0), 7.74 (ddd, 1, J = 0.8, 1.2, 8.0).

(b) Preparation of 3-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzo(b)thiophene-2-carboxamide hydrochloride

3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.6 g, 8.96 mmol) (Example 1(b)) and anhydrous chloroform (20 mL) were added to a 100-mL, round-bottomed flask and stirred under N_2. A solution of trimethylaluminum (4.6 mL, 9.2 mmol, 1.03 eq) (Aldrich Chemical Company, 2.0 M in toluene) was slowly added to the reaction mixture and the pale yellow solution was stirred under N_2 for 20 min. Another portion of trimethylaluminum (4.6 mL, 9.2 mmol, 1.03 eq) was added to the reaction mixture. A solution of methyl 3-aminobenzo[b]thiophene-2-carboxylate (1.86 g, 8.98 mmol, 1.0 eq) in anhydrous chloroform (10 mL) was added to the reaction mixture and stirred under N_2 at room temperature for 0.5 h. The golden-yellow solution was heated at 40 °C for 4 days. The oil bath was removed and the dark orange solution was allowed cool. To the slightly warm reaction mixture was slowly added 1 N HCl (50 mL). The acidic reaction mixture was heated at 40 °C for 0.5 h. The reaction mixture was allowed to cool and saturated K_2CO_3 was added. The reaction mixture was transferred to a separatory funnel and extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered and concentrated to give the crude product as an orange liquid. The free base was purified by flash chromatography with a gradient eluant of dichloromethane (100-95%): methanol (0-5%) to give 1.14 g (27%) of the free base as an orange oil. The free base 1.05 g (2.25 mmol) was dissolved in ethyl acetate and 2.25 mL of 1 N ethereal HCl (1.0 eq) was added. The hydrochloride salt was recrystallized from ethanol / water to give 0.82 g (18%) of the title compound as a beige solid. mp: 242-244 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.76 (m, 2), 3.10-3.50 (m, 8), 3.59 (br d, 2, J = 11.2), 4.08 (br d, 2, J = 13.4), 7.07 (br s, 2), 7.38 (ddd, 1, J = 1.1, 7.1, 8.1), 7.47 (tm, 2, J = 7.6), 7.60 (ddd, 1, J = 1.1, 7.1, 8.2), 7.68 (br t, 1, J = 5.6), 7.83 (d, 1, J = 7.7), 8.03 (d, 1, J = 7.9), 8.12 (t, 2, J = 8.3), 10.39 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.61, 27.61, 39.10, 47.33, 51.40, 56.16, 99.33, 122.16, 123.48, 123.94, 124.75, 124.98, 125.59, 127.93, 128.49, 129.08, 133.38, 137.89, 148.29, 153.09, 163.20, 166.12.

Anal. Calcd for $C_{24}H_{27}N_5OS_2 \cdot HCl$: C, 57.41; H, 5.62; N, 13.95. Found: C, 57.42; H, 5.68; N, 13.94.

Example 12

(a) Preparation of 2-cyano-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)acetamide

3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.23 g, 7.69 mmol (Example 1(b)), cyanoacetic acid (0.76 g, 8.93 mmol, 1.16 eq) (Aldrich Chemical Company) and N,N-dimethylformamide (20 mL) were added to a 250-mL, round-bottomed flask, and stirred under N_2. A solution of 1,3-dicyclohexylcarbodiimide (1.86 g, 9.01 mmol, 1.17 eq) (Aldrich Chemical Company) in N, N-dimethylformamide (5 mL) was added dropwise to the reaction mixture. 1-Hydroxybenzotriazole hydrate (1.24 g, 9.18 mmol, 1.19 eq) (Aldrich Chemical Company) was added and the reaction mixture was allowed to stir at room temperature under N_2 for 23 h. The suspension was filtered and the solid was washed with N, N-dimethylformamide. The filtrate was concentrated to give an orange oil. The crude free base was dissolved in ethyl acetate and filtered. The filtrate was applied directly to a silica gel column and partially purified by flash chromatography with a gradient eluant of ethyl acetate (90-80%) : methanol (10-20%) to give 2.92 g of the crude product as an orange oil. The crude free base was dissolved in dichloromethane and washed with saturated K_2CO_3. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 1.93 g (70%) of the title compound as a pale beige solid. ^1H NMR ($CDCl_3$): d, 1.63 (br t, 4, J = 3.3), 2.47 (br t, 2, J = 6.7), 2.69 (br t, 4, J = 4.9), 3.36 (m, 2), 3.37 (s, 2), 3.57 (br t, 4, J = 4.9), 6.66 (br s, 1), 7.36 (ddd, 1, J = 1.2, 7.0, 8.1), 7.47 (ddd, 1, J = 1.2, 6.9, 8.2), 7.82 (dt, 1, J = 7.8, 1.1), 7.91 (dm, 1, J = 8.0).

(b) Preparation of 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-thiophenecarboxamide

2-Cyano-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)acetamide (1.83 g, 5.12 mmol), 1,4-dithiane-2,5-diol (1.79 g, 11.8 mmol, 2.30 eq) (Aldrich Chemical Company), triethylamine (1.70 mL, 1.23 g, 12.2 mmol, 2.38 eq) and ethanol (30 mL) were added to a 500-mL, round-bottomed flask, and heated at 60-65 °C under a nitrogen atmosphere for 3 h. The oil bath was removed and the reaction mixture was allowed to

cool. Water and dichloromethane were added and the reaction mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give a red-brown residue. The crude free base was partially purified by flash chromatography with a gradient eluant of ethyl acetate (100-98%): methanol (0-2%) to give a partially solidified orange oil. The free base was dissolved in ethyl acetate and filtered. The filtrate was partially concentrated to give a suspension. The pale tan solid was filtered and dried to give 0.239 g (11%) of the title compound. mp: 155-159 °C (dec). ^1H NMR ($CDCl_3$): δ, 1.68 (br s, 4), 2.48 (br s, 2), 2.68 (br s, 4), 3.42 (m, 2), 3.58 (br s, 4), 5.84 (br s, 1), 6.07 (br s, 2), 6.23 (d, 1, J = 5.8), 6.71 (br d, 1, J = 5.8), 7.35 (ddd, 1, J = 1.1, 7.0, 8.1), 7.46 (ddd, 1, J = 1.1, 7.0, 8.1), 7.81 (d, 1, J = 8.2), 7.90 (d, 1, J = 8.2). ^{13}C NMR (DMSO-d_6): δ 23.80, 27.47, 38.26, 49.61, 52.53, 57.61, 105.69, 107.55, 121.09, 124.18, 124.22, 124.43, 127.40, 127.89, 152.06, 161.05, 163.52, 165.45.

Anal. Calcd for $C_{20}H_{25}N_5OS_2 \cdot 3/20\ C_4H_8O_2 \cdot 0.3\ H_2O$ C, 56.98; H, 6.22; N, 16.13. Found: C, 56.70; H, 6.15; N, 16.26.

Example 13

(a) Preparation of N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-8-quinolinecarboxamide hydrochloride

Anhydrous N,N-dimethylformamide (20 mL), 8-quinolinecarboxylic acid (1.04 g, 6.01 mmol) (Aldrich Chemical Company), 1-hydroxybenzotriazole hydrate (0.898 g, 6.65 mmol, 1.11 eq) (Aldrich Chemical Company) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.75 g, 6.03 mmol, 1.0 eq) (Example 1(b)) were combined in a 250-mL round-bottomed flask. The reaction mixture was cooled in an ice-water bath and stirred under N_2. A solution of 1,3-dicyclohexylcarbodiimide (1.37 g, 6.64 mmol, 1.10 eq) (Aldrich Chemical Company) in anhydrous N,N-dimethylformamide (12 mL) was added dropwise to the reaction mixture. The ice-water bath was removed and the reaction mixture was stirred at room temperature for 20 h. The suspension was concentrated *in vacuo* and the crude product was partitioned between ethyl acetate and saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined.

dried over $MgSO_4$, filtered and concentrated to give a mixture of finely dispersed solids in an orange oil. Ethyl acetate was added to the mixture and the suspension was filtered. The filtrate was concentrated to give 2.98 g of the crude product as an orange oil. The crude product was purified by flash chromatography with dichloromethane, dichloromethane:methanol (99:1) and dichloromethane:methanol (97:3) as eluant. The appropriate fractions were combined, concentrated, redissolved in dichloromethane, filtered and concentrated to give 1.46 g of the free base as a yellow oil. The free base was dissolved in dichloromethane and 1N ethereal HCl (3.28 mL, 1.0 eq) was added. The solvent was removed *in vacuo*. The resulting hydrochloride salt was dissolved in methanol and the solution was filtered through fluted filter paper directly into rapidly stirred ethyl acetate. The suspension was filtered to give 0.265 g of the title compound as a pale beige solid. The filtrate was concentrated and recrystallized from methanol to give a second crop (0.447 g) for a total yield of 0.712 g (25%). mp: 187-189 °C. ^1H NMR (DMSO-d6): δ 1.68 (m, 2), 1.91 (m, 2), 3.10-3.42 (m, 4), 3.56 (m, 6), 4.03 (br d, 2, J = 11.8), 7.43 (t, 1, J = 7.5), 7.56 (t, 1, J = 7.6), 7.65 (dd, 1, J = 4.3, 8.3), 7.72 (t, 1, J = 7.7), 8.09 (t, 2, J = 7.7), 8.17 (δ, 1, J = 8.1), 8.54 (dm, 2, J = 7.6), 9.09 (dd, 1, J = 1.4, 4.1), 10.87 (br t, 1, J = 5.5), 11.55 (br s, 1). ^{13}C NMR (DMSO-d6): δ 21.24, 26.95, 38.85, 46.72, 50.82, 55.59, 121.52, 121.90, 124.35, 124.94, 126.66, 127.31, 128.44, 128.56, 129.67, 132.38, 132.72, 138.30, 144.99, 150.82, 152.43, 162.60, 165.41.

Example 14

(a) Preparation of 1,2,3,4-Tetrahydro-8-quinolinecarboxylic acid

This compound was prepared according to the method described by Coppola, G.M. (*J. Heterocyclic Chem.*, **1978**, *15*, 645) by employing 8-quinolinecarboxylic acid (1.73 g, 9.99 mmol) (Aldrich Chemical Company), platinum oxide hydrate (0.182 g) (EM Science) and ethanol (30 mL). The mixture was hydrogenated on a Parr hydrogenator at 50 psi for 2 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to give 1.76 g (99%) of the title compound as a pale yellow solid. mp: 158-160 °C. [lit. mp: 165-167 °C]. ^1H NMR (DMSO-d6): δ 1.77 (quin, 2, J = 5.9), 2.69 (t, 2, J = 6.2), 3.33 (t, 2, J = 5.5), 6.36 (t, 1, J = 7.5), 7.00 (d, 1, J = 7.0), 7.54 (d, 1, J = 8.0). ^{13}C NMR (DMSO-d6): δ 21.46, 28.33, 41.68, 109.59, 114.17, 122.73, 130.58, 134.54, 149.13, 171.24.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.56; H, 6.32; N, 7.85.

(b) Preparation of N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2,3,4-tetrahydro-8-quinolinecarboxamide

This compound was prepared according to the method described for Example 13(a) by employing 1,2,3,4-tetrahydro-8-quinolinecarboxylic acid (1.06 g, 5.98 mmol), 1-hydroxybenzotriazole hydrate (0.90 g, 6.66 mmol, 1.1 eq) (Aldrich Chemical Company), 1,3-dicyclohexylcarbodiimide (1.47 g, 7.12 mmol, 1.2 eq) (Aldrich Chemical Company), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.82 g, 6.27 mmol, 1.05 eq) (Example 1(b)) and anhydrous N,N-dimethylformamide. The reaction mixture was allowed to stir at room temperature for 18h, concentrated *in vacuo*, and the crude product was partitioned between dichloromethane and saturated $NaHCO_3$. The finely dispersed solids were filtered and the filtrate was concentrated to give the crude free base. This material was purified by flash chromatography as described in Example (13a). The purified free base (2.28 g, 5.07 mmol) was dissolved in dichloromethane and 1N ethereal HCl (5.07 mL, 1.0 eq) was added. The solvent was removed *in vacuo* and the resulting hydrochloride salt was dissolved in MeOH. The solution was filtered through a fluted filter paper directly into rapidly stirred ethyl acetate. The suspension was filtered to give 0.28 g (9%) of the title compound as an orange-beige solid. mp: 138-142 °C. ^1H NMR (DMSO-d_6): δ 1.55 (m, 2), 1.77 (m, 4), 2.69 (t, 2, J = 6.0), 3.21 (m, 8), 3.47 (t, 2, J = 12.9), 3.56 (d, 2, J = 11.6), 4.05 (d, 2, J = 13.4), 4.46 (br s, 1), 6.44 (t, 1, J = 7.5), 6.96 (d, 1, J = 7.0), 7.37 (d, 1, J = 7.8), 7.46 (t, 1, J = 7.5), 7.58 (t, 1, J = 7.5), 8.11 (t, 2, J = 8.2), 8.32 (br t, 1, J = 5.3), 10.91 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.54, 21.86, 27.43, 28.27, 39.11, 41.75, 47.56, 51.64, 56.34, 115.14, 115.19, 122.37, 123.35, 125.15, 125.78, 127.35, 128.10, 129.29, 132.84, 146.19, 153.26, 163.35, 170.20.

Anal. Calcd for $C_{25}H_{31}N_5OS \cdot 1.5\ HCl \cdot 0.35\ H_2O$: C, 58.81; H, 6.55; N, 13.72; Cl, 10.41; H_2O, 1.23. Found: C, 58.47; H, 6.62; N, 13.43; Cl, 10.18; H_2O, 0.85.

Example 15

(a) Preparation of 2-(2,3-Dihydro-1*H*-indol-1-yl)glyoxyloyl chloride

This compound was prepared according to the procedure described by Welstead, W.J., *et al.* (*J. Med. Chem.* 1979, *22*, 1074) with modifications. Oxalyl chloride (102.1 g, 0.804 mol) (Aldrich Chemical Company) and anhydrous dichloromethane (400 mL) were added to a 2-L, 3-necked round-bottomed flask. The flask was equipped with a mechanical stirrer, addition funnel and N_2 inlet. A solution of indoline (48.0 g, 0.403 mol) in anhydrous dichloromethane (350 mL) was added dropwise to the stirred reaction mixture over a 2h period. The reaction mixture was stirred at room temperature for 3 h and then allowed to stand overnight. The resulting red-brown solution was concentrated and diethyl ether was added to the residue. The suspension was filtered and the filtrate was concentrated to give 56.75 g (68%) of the acid chloride as a yellow-green solid. The crude acid chloride was used without further purification. ^{1}H NMR (DMSO-d6): δ 3.19 (t, 2, J = 8.3), 4.17 (t, 2, J = 8.3), 7.12 (t, 1, J = 6.9), 7.24 (t, 1, J = 7.1), 7.33 (d, 1, J = 7.0), 8.01 (d, 1, J = 7.6).

(b) Preparation of 4,5-dihydropyrrolo[3,2,1-hi]indoline-1,2-dione

Aluminum chloride (12.7 g, 95.2 mmol, 5.0 eq) (Aldrich Chemical Company) and 2-(2,3-dihydro-1H-indol-1-yl(glyoxyloyl)chloride (4.00 g, 19.1 mmol) were added to a 300-mL round-bottomed flask equipped with a magnetic stir bar and N_2 inlet. The mixture was quickly heated to 100-120°C and allowed to stir for 20 min. The oil bath was removed and the mixture was allowed to cool to room temperature. The resulting solid was broken up with a spatula and added to ice-water (600 mL). The aqueous mixture was stirred for 1 hr and extracted with chloroform. The organic layer was dried over $MgSO_4$, filtered and concentrated to give an oily red residue. The residue was triturated with acetone and filtered to give 0.71 g (22%) of the title compound as a red solid. mp: 203-207 °C [lit. (Welstead, W.J., *et al., J. Med. Chem.* 1979, *22*, 1074) mp: 206-208 °C]. ^{1}H NMR (DMSO-d6): δ 3.36 (t, 2, J = 7.9), 4.06 (t, 2, J = 7.9), 6.95 (t, 1, J = 7.5), 7.24 (d, 1, J = 7.6), 7.46 (d, 1, J = 7.1). ^{13}C NMR (DMSO-d6): δ 31.35, 46.88, 113.03, 122.72, 124.74, 126.22, 134.16, 156.45, 160.67, 184.71.

Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.09; H, 4.10; N, 8.00.

(c) Preparation of indoline-7-carboxylic acid

A solution of sodium hydroxide (1.82 g in 20.2 mL of water) and 4,5-dihydropyrrolo[3,2,1-hi]indoline-1,2-dione (1.0 g, 5.8 mmol) were combined in a 100-mL round-bottomed flask and stirred at room temperature for 30 min. A solution of hydrogen peroxide (1.82 mL of 30% H_2O_2 in 18.2 mL H_2O) was added dropwise and the reaction mixture was allowed to stir for 3.5 h. The reaction mixture was transferred to a separatory funnel and washed with benzene. The aqueous layer was separated, the pH was adjusted to 6-7 by the addition of 1N HCl and the solution was extracted with chloroform. The pH of the aqueous layer was adjusted to 4-5 by the addition of 1N HCl and extracted with an additional portion of chloroform. The organic layers were dried over $MgSO_4$, filtered and concentrated to give a gold-tan solid. The crude product was triturated with benzene:isooctane (3:1) to give 0.54 g (57%) of the title compound as a tan solid. mp: 164-166 °C. [lit. (Welstead, W.J., *et al., J. Med. Chem.* **1979**, *22*, 1074) mp: 164-168 °C]. ^{1}H NMR (DMSO-d_6): δ 2.93 (t, 2, J = 8.6), 3.55 (t, 2, J = 8.6), 6.44 (t, 1, J = 7.0), 7.13 (d, 1, J = 6.9), 7.36 (d, 1, J = 7.5). ^{13}C NMR (DMSO-d_6): δ 28.19, 46.70, 107.95, 115.49, 128.14, 128.43, 131.26, 154.48, 168.73.

Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.98; H, 5.51; N, 8.48.

(d) Preparation of *N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-2,3-dihydro-1*H*-indole-7-carboxamide

This compound was prepared according to the method described for Example 13(a) by employing indoline-7-carboxylic acid (0.86 g, 5.27 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.60 g, 5.51 mmol, 1.05 eq) (Example 1(b)), 1-hydroxybenzotriazole hydrate (0.78 g, 5.77 mmol, 1.10 eq) (Aldrich Chemical Company), 1,3-dicyclohexylcarbodiimide (1.35 g, 6.54 mmol, 1.24 eq) (Aldrich Chemical Company) and anhydrous N,N-dimethylformamide. The reaction mixture was allowed to stir at room temperature for 24 h, and the solvent was removed *in vacuo*. Ethyl acetate was added to the residue and the mixture was filtered to remove the insoluble material. The filtrate was washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 3.12 g of the crude product as an orange oil. The crude material was purified by flash chromatography with ethyl acetate:methanol (99:1) followed by ethyl acetate:methanol (97:3) as eluant. The appropriate fractions were combined, concentrated, redissolved in dichloromethane,

filtered and concentrated to give 0.96 g (42 %) of the title compound as an orange oil. ^{1}H NMR (DMSO-d6): δ 1.51 (m, 4), 2.36 (t, 2, J = 6.4), 2.56 (br t, 4, J = 4.5), 2.89 (t, 2, J = 8.6), 3.22 (br q, 2, J = 6.0), 3.41 (br t, 4, J = 4.5), 3.51 (t, 2, J = 8.6), 6.45 (t, 1, J = 7.5), 6.54 (s, 1), 7.07 (d, 1, J = 7.2), 7.35 (d, 1, J = 8.1), 7.41 (tm, 1, J = 7.5), 7.53 (tm, 1, J = 7.5), 8.02 (d, 1, J = 8.1), 8.03 (d, 1, J = 8.2), 8.11 (t, 1, J = 5.6).

Example 16

(a) Preparation of 1*H*-indole-7-carboxylic acid

This compound was prepared according to the method described by Ikan, R. and Rapaport, E. (*Tetrahedron*, **1967**, *23*, 3823) by employing indoline-7-carboxylic acid (3.0 g, 18.4 mmol) (Example 15(c)), 10% Pd on carbon (0.75 g) (Aldrich Chemical Company) and xylenes (150 mL). The reaction mixture was heated for 4 h. The hot solution was filtered through a pad of celite and the filtrate was concentrated to give 1.55 g (52%) of the title compound as a red-beige solid. mp: 202-204 °C [lit. 202 °C]. ^{1}H NMR (DMSO-d6): δ 6.52 (dd, 1, J = 2.0, 3.0), 7.08 (t, 1, J = 7.7), 7.35 (t, 1, J = 2.8), 7.74 (dd, 1, J = 1.2, 7.5), 7.81 (d, 1, J = 7.9), 11.05 (s, 1), 12.98 (br s, 1). ^{13}C NMR (DMSO-d6): δ 101.80, 113.83, 118.70, 124.13, 125.97, 127.16, 129.61, 134.90, 168.31.

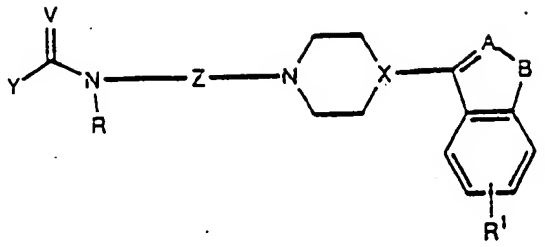
(b) Preparation of *N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1*H*-indole-7-carboxamide

This compound was prepared according to the method described for Example 13(a) by employing 1*H*-indole-7-carboxylic acid (1.32 g, 8.19 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.47 g, 8.51 mmol, 1.04 eq) (Example 1(b)), 1-hydroxybenzotriazole hydrate (1.20 g, 8.88 mmol, 1.08 eq) (Aldrich Chemical Company), 1,3-dicyclohexylcarbodiimide (1.87 g, 9.06 mmol, 1.1 eq) (Aldrich Chemical Company) and anhydrous N,N-dimethylformamide. The reaction mixture was allowed to stir at room temperature for 16 h and the solvent was removed *in vacuo*. Ethyl acetate was added to the residue and the suspension was filtered. The filtrate was washed with saturated $NaHCO_3$ and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product as an orange oil. The crude free base was purified by flash chromatography with ethyl acetate, ethyl acetate:methanol (99:1) and ethyl acetate:methanol (97:3) as eluant to give 3.27 g (92 %) of the title compound as a yellow oil. ^{1}H NMR (DMSO-d6): δ 1.57 (m, 4), 2.39 (t,

2, J = 6.9), 2.57 (br t, 4, J = 4.5), 3.35 (m, 2), 3.42 (br t, 4, J = 4.5), 6.46 (t, 1, J = 2.9), 7.04 (t, 1, J = 7.6), 7.32 (t, 1, J = 2.9), 7.41 (tm, 1, J = 7.6), 7.53 (tm, 1, J = 7.8), 7.64 (d, 1, J = 7.5), 7.70 (d, 1, J = 8.1), 8.02 (d, 1, J = 8.1), 8.03 (d, 1, J = 8.2), 8.53 (t, 1, J = 5.6), 11.13 (s, 1).

CLAIMS

1. A compound of formula I.



(I)

wherein Y is a heteroaryl group optionally substituted by one or more halogen, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, aryloxy, arylC_{1-6}alkylenoxy, hydroxy, $S(O)_nR^2$ or $S(O)_nN(R^2)_2$ where n is 0, 1 or 2, CN, $CON(R^2)_2$, COR^2, CO_2R^2, CO-aryl, azido, $-N(R^2)_2$,$-NR^2N(R^{2a})_2$, $-NR^2N=C(R^{2a})_2$, $-NR^2(C=O)CH(N(R^{2a})_2)R^{2b}$, $-NR^2(C=O)R^{2a}$, $NR^2CO_2R^{2a}$, C_{1-6}alkoxycarbonylamino or PhN=N;
with the proviso that Y does not include benzisothiazolyls or benzisoxazolyls,
V is O or S;
Z is C_{1-8}alkylene optionally interrupted by -O- or $-S(O)_n-$ where n is 0, 1 or 2, C_{2-8}alkenylene or C_{2-8}alkynylene;
X is N, CR^3 or COR^3;
A is CR^4 or N;
B is oxygen, NR^5 or $S(O)_n$, where n is 0, 1 or 2; and
R^1 is hydrogen or one or more halogen, hydroxy, nitro, CN, NR^6_2, C_{1-6}alkoxy, aryloxy, arylC_{1-6}alkylenoxy, or COR^6,
R, R^2, R^{2a}, R^{2b}, R^3, R^4, R^5 and R^6, are each hydrogen or C_{1-6}alkyl;
or a salt, solvate, N-oxide or physiologically functional derivative thereof.

2. A compound, salt, solvate, N-oxide or derivative according to Claim 1 wherein the heteroaryl group is selected from the group comprising:
pyridinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, pyridazinyl, quinolinyl, isoquinolinyl, imidazolyl, benzimidazole, furyl, benzofuryl, thienyl, benztheinyl, indazolyl, oxazolyl, thiazolyl, isothiazolyl, isoxazolyl, purinyl, triazinyl, indolyl.

napthiridinyl, quinazolinyl, pyrrolopyridinyl, tetrahydroquinolinyl, indolinyl, quinoxalinyl, triazolyl or thiadiazolyl.

3. A compound, salt, solvate, N-oxide or derivative according to either of Claims 1 and 2, wherein the heteroaryl group is substituted with $N(R^2)_2$.

4. A compound, salt, solvate, N-oxide or derivative according to any of Claims 1 to 3 wherein the heteroaryl group is pyridine, thiophene or benzthiophene, optionally substituted with NH_2, NHMe or NHAc and R is H or Me.

5. A compound, salt, solvate, N-oxide or derivative according to any of Claims 1 to 4, wherein R is H and the heteroaryl group is pyridine or thiophene substituted with NH_2.

6. The compounds:

N-(4-(4-(1,2,Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide;
N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide;
N-(4-(4-(1,2,Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-pyridinecarboxamide;
t-Butyl N-(4-(N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)-3-thienyl)carbamate;
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-pyridinecarboxamide;
4-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-thiophenecarboxamide;
4-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-thiophenecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)benzo(b)thiophene-2-carboxamide;

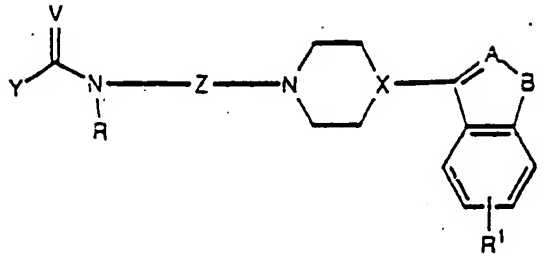
2-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-thiophenecarboxamide;
N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-8-quinolinecarboxamide;
N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2,3,4-tetrahydro-8-quinolinecarboxamide;
N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-2,3-dihydro-1H-indole-7-carboxamide;
N-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl]-1H-indole-7-carboxamide;
and physiologically acceptable salts, solvates, physiologically functional derivatives and N-oxides thereof.

7. The compounds:

3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-thiophenecarboxamide;
N-(4-(4-(1,2,Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide;
N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide;
and physiologically acceptable salts, solvates, physiologically functional derivatives and N-oxides thereof.

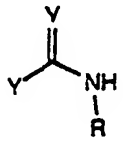
8. 3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide; and physiologically acceptable salts, solvates, physiologically functional derivatives and N-oxides thereof.

9. A process of preparing a compound of formula (I):



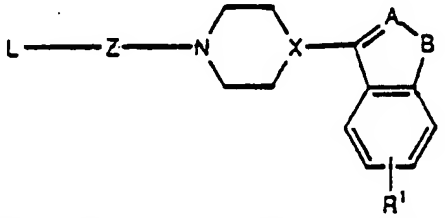
(I)

wherein Y, V, Z, X, A, B, R, R^1, R, R^2, R^{2a}, R^3, R^4, R^5, and R^6 are as defined in any one of Claims 1 - 9 or a salt, solvate, N-oxide or physiologically functional derivative thereof, comprising the reaction of a compound of formula II.



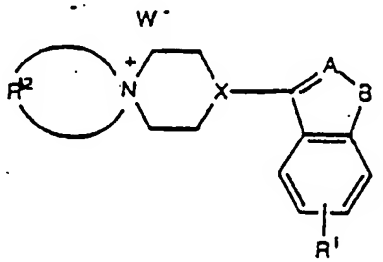
(II)

with a compound of formula (III)



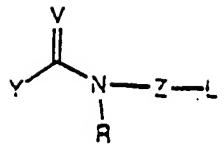
(III)

wherein L is a leaving group or by reaction of a compound of formula (II) with a compound of formula (IV)



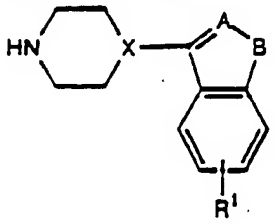
(IV)

wherein W^- is a suitable anion and R^{12} is $-(CH_2)_4$ or $-(CH_2)_5$ or by reaction of a compound of formula (V)



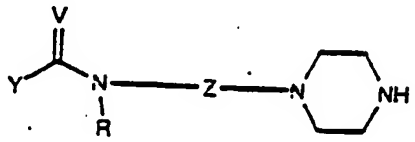
(V)

in which L is a leaving group, with a compound of formula (VI)



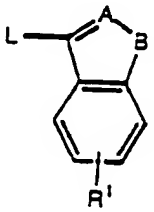
(VI)

or by reaction of a compound of formula VII



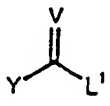
(VII)

with a compound of formula (VIII)



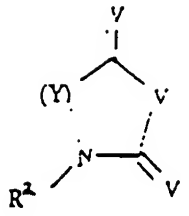
(VIII)

in which L is as hereinbefore defined,
or by reaction of compounds of formula (IX) or (IXa)



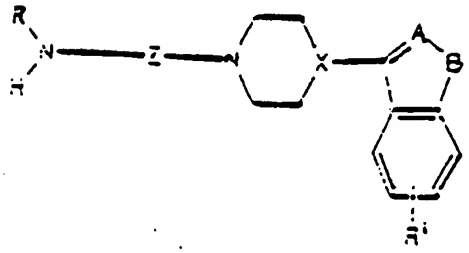
(IX)

wherein L^1 is a halogen OMe or OH



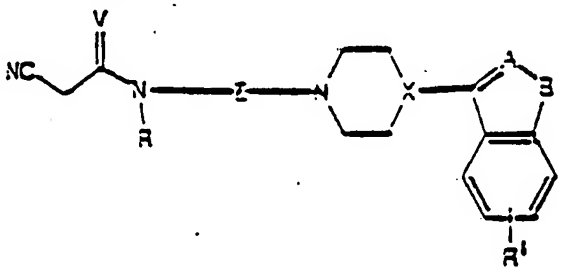
(Xa)

and wherein Y, V and R^2 are as previously described, with a compound of formula (X)



(X)

or by treatment of a compound of formula (Xa)



(Xa)

with 1,4-dithiane-2,5-diol

or by reduction of a compound of formula (I) in which Z is C_{2-8}alkenylene or C_{2-8} alkynylene.

or by hydrolysin of the corresponding alkoxycarbonylamino derivative of a compound of formula (I) which is optionally substituted by one or more $N(R^2)_2$ or $NRN(R^2)_2$.

10. A compound of formula (I) as defined in Claim 1, or a physiologically acceptable salt, solvate, N-oxide or physiologically functional derivative thereof, for use in therapy.

11. The use of any of the following compounds, or physiologically acceptable salts, solvates, N-oxides or physiologically functional derivatives thereof, in therapy

3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-pyridinecarboxamide;
3-Amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-thiophenecarboxamide;
N-(4-(4-(1,2,Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide;
N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide;
and physiologically acceptable salts, solvates, physiologically functional derivatives and N-oxides thereof.

12. The use of a compound of formula (I) as defined in Claim 1 or a physiologically acceptable salt, solvate, N-oxide or physiologically functional derivative thereof for the manufacture of a medicament for the treatment or prophylaxis of a psychotic disorder.

13. Use according to Claim 12 wherein the psychotic disorder is schizophrenia.

14. A pharmaceutical composition comprising a compound of formula (I) as defined in Claim 1, or a physiologically acceptable salt, solvate, N-oxide or physiologically functional derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 94/00265

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D417/12 C07D417/14 A61K31/425 A61K31/445 A61K31/42
C07D413/12 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 511 610 (HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED) 4 November 1992 cited in the application see claims ---	1,10, 12-14
Y	EP,A,0 512 755 (JOHN WYETH AND BROTHER LIMITED) 11 November 1992 see claims ---	1,10, 12-14
Y	EP,A,0 261 688 (SUMITOMO PHARMACEUTICALS COMPANY LIMITED) 30 March 1988 see claims ---	1,10, 12-14
Y	EP,A,0 196 096 (SUMITOMO PHARMACEUTICALS COMPANY LIMITED) 1 October 1986 see claims -----	1,10, 12-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 1994	27. 05. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/GB 94/00265

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		US-A-	4948799	14-08-90
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		AU-A-	5527686	02-10-86
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		US-A-	4745117	17-05-88